





MONOGRAPHS

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*The Cancer Information Service:
A 15-Year History of Service and Research*
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FOREWORD

"I have called several times over the last 1½ years and each time I have been struck by the patience, cooperation, and knowledge of the person I spoke with. I have found each time a real willingness to help locate and communicate information. . . . I have always felt the person not only had an understanding of cancer as a disease but also understood that the caller may be anxious or confused and need extra time to absorb information."—Letter to the Cancer Information Service (CIS)

I wanted to share this letter as I couldn't express the importance of the CIS better myself. Working here at the National Cancer Institute (NCI), I have the very best information on cancer prevention, diagnosis, and treatment at my fingertips. The miracle of the CIS is that anyone—patient, family, or health-care provider—can obtain the most up-to-date information on cancer and cancer treatment and that this information is as close as the famous 1-800-4-CANCER toll-free telephone number. In many cases, a call can save a life or greatly ameliorate suffering. This service directly benefits the American people all across the country.

We need every weapon against cancer, and information can be a powerful, lifesaving tool. That is the strength of the CIS. This monograph gives the history of the CIS—a program created out of a need to help cancer patients and their families. It also describes the evolution of the CIS to a sophisticated system that supports 19 regional offices and rigorously trains information specialists. The CIS has pioneered information dissemination and health education, it acknowledges the right of the patient to have state-of-the-art information, and it has helped to change the way not only oncology, but medicine in general, is practiced in the United States. But the fundamental truth about the value of the CIS lies not in its complexity, but in its simplicity. A call is made, a question is answered. NCI reaches out through the CIS, and the CIS is the voice of NCI.

The people who have created and championed the CIS and the people who staff it deserve to be very proud.

Samuel Broder, M.D.
Director, NCI

Introduction

Alfred C. Marcus, Erwin P. Bettinghaus, Kate Duffy Mazan, Marion E. Morra, Eleanor O'D. Nealon, J. Paul Van Nevel*

In mid-1991, the editors convened the first of what was to become a seemingly endless succession of weekly telephone conference calls to discuss, coordinate, and facilitate the production of a special National Cancer Institute (NCI) monograph dedicated to the Cancer Information Service (CIS). The CIS was implemented in 1975 by NCI to disseminate accurate, up-to-date information about cancer to cancer patients, the relatives and friends of cancer patients, health-care professionals, and the general public. This monograph is intended to serve as a 15-year retrospective of this remarkable information and education program.

At the outset, the editors identified three primary objectives of the monograph. First, it should provide a comprehensive overview of the CIS. During the past 15 years, a substantial body of historical and descriptive information about the CIS has been generated, along with an impressive accumulation of program evaluation data. Much of this information was dispersed across a wide range of sources, including journal articles and other publications, presentations made at various professional meetings and conferences, and numerous internal memoranda and other related documents at NCI. One of the primary objectives of this monograph was to distill and organize this formidable body of information and publish it in a form that could serve as a general resource for health-care professionals, clinical and behavioral scientists, cancer communication specialists, public-health officials, and policy-makers.

The second objective of this monograph was to increase awareness of the CIS among these same constituencies. The CIS has a unique story, both in terms of its overall and specific accomplishments as a major service-delivery and community outreach arm of NCI and in terms of its service as a highly significant and productive laboratory for cancer communications research within the United States. The lessons learned over the past 15 years need to be disseminated and shared, so that others can profit from this unique social experiment in information and technology transfer at NCI.

The third and final objective was to provide programmatic and policy guidance to NCI. The CIS will soon enter its third decade of continuous service to the nation. To plan adequately and appropriately for the future, it is necessary to understand the unique history and ongoing evolution of the CIS as a dynamic system and the opportunities that exist for continued refinements and improvement in service delivery. Thus, the contributing authors to this monograph were challenged to distill in their papers

key recommendations or issues that should be considered by NCI as CIS programs, policies, and research continue to evolve over time.

BRIEF OVERVIEW OF THE CIS

To provide a general context for the papers published in this monograph, it is important to begin with a common reference point with respect to the goals and objectives of the CIS, as well as its primary methods of operation. As noted above, the CIS was implemented to disseminate to the nation accurate, up-to-date information with respect to cancer prevention, screening and early diagnosis, treatment, rehabilitation, and continuing care. The public-health mandate of the CIS is grounded in the National Cancer Act of 1971 and the amendments to that act made over the past 20 years. For example, the 1971 act stipulated that NCI "Provide a program to disseminate and interpret . . . for practitioners and other health professionals, scientists, and the general public, scientific and other information regarding the causes, prevention, detection, and treatment of cancer." The specific goals and objectives of the CIS have evolved over time in response to this 20-year mandate. The most recent articulation of these goals and objectives is summarized in Table 1.

As noted in Table 1, the CIS has attempted to achieve its major goals by establishing and maintaining a network of regional offices that are typically linked to NCI-funded regional cancer centers. Although the specific configuration of the regional offices has changed with each CIS contract renewal, most of the CIS offices have been in existence for a decade or longer.

As shown in Fig. 1, the CIS is currently administered by the Office of Cancer Communications (OCC) at NCI. OCC, in turn, coordinates and supervises the activities of the regional CIS network, which disseminates cancer information using two major strategies: 1) respond to requests for information over the telephone and 2) conduct community outreach activities. The community outreach programs of the CIS can be further divided into mass-media campaigns that promote use of the CIS toll-free telephone number and/or encourage specific cancer prevention and control behaviors (e.g., smoking cessation or screening mammography) and more interpersonal community outreach efforts conducted by CIS staff.

*See "Notes" section following "Acknowledgments."

Table 1. Overview of major goals and objectives of the CIS**Goals*

- To use communication strategies to reduce cancer incidence, morbidity, and mortality.
- To provide NCI-designated cancer centers and other major community cancer organizations and intermediaries with a resource for developing outreach programs to reach their various audiences.
- To establish a high-quality system that can serve as a resource and a database for stimulating the development and implementation of new research projects in cancer communications.

Objectives

- To support a network of regional CIS offices throughout the country that will serve as local outlets for NCI to disseminate information on cancer to communities and serve as catalysts for the adoption and adaptation of NCI, OCC education programs, materials, and messages in the community.
- To operate a toll-free telephone service in the regional offices. . . .
- To mobilize local media and community-based organizations to use and adopt OCC programs, materials, and messages in support of NCI education initiatives.
- To establish reliable data-collection strategies and dissemination techniques to facilitate evaluation of the role of communication strategies in reducing morbidity and mortality from cancer.

*Abstracted from the Cancer Information Service Request for Contract Proposals, January 3, 1992; National Cancer Institute, National Institutes of Health.

The major channel used by the CIS to disseminate cancer information to the nation is the telephone. Thus, each regional CIS office is staffed by highly trained information specialists who answer the inquiries of callers to the CIS. Additional resources available in each regional CIS office to support the work of the information specialists (see Fig. 1) include a library of NCI-approved print material (these materials are often mailed to callers as a follow-up service of the CIS); the Physician Data Query (PDQ) computerized database, which provides information on state-of-the-art cancer treatment and clinical trials to physicians and patients; various resource materials and directories that are consulted by CIS information specialists; and local subject-matter specialists who are also consulted on an as-needed basis. The resource directories used by the information specialists are continually updated by the regional CIS network to ensure that accurate referral information is provided to CIS callers. As noted elsewhere in this monograph (1), with few exceptions CIS call volume has increased steadily each year since 1976. Especially noteworthy is the total call volume aggregated across all years: more than 5 million calls received by the CIS between 1976 and 1992. Currently, call volume to the CIS exceeds 500 000 calls per year.

All CIS offices adhere to a standard set of operational guidelines determined by NCI, guidelines that since 1983 have included the completion of a standardized Call

Record Form (CRF) for each call handled by an information specialist. The CRFs include specific questions regarding the nature of the inquiry—the type of caller (e.g., cancer patient, friend or relative of cancer patient, health-care professional, general public); how the caller found out about the CIS; the specific recommendations made to the caller by the information specialist; and the length of the call. Historically, a 20% random sample of callers has also been asked selected demographic questions, including age, gender, race/ethnicity, and educational attainment. Since 1983, nearly 3 million CRFs have been completed by CIS information specialists. Many of the papers in this monograph have drawn on this exceedingly rich database for analysis and program evaluation.

Although the telephone is the primary channel for disseminating information about cancer to the nation, the CIS is much more than a telephone-based information system. As indicated in Fig. 1, the CIS assists OCC in its efforts to develop, produce, and coordinate education initiatives to promote specific cancer-control behaviors within defined populations. OCC education initiatives typically include public service announcements and video news releases for the electronic media and press releases and clip sheets for the print media. Regional CIS offices routinely assist OCC in conducting these campaigns by coordinating efforts in their regions. These efforts include contacting local media to encourage use of OCC materials based on specific local needs; initiating special programs on television and radio; arranging for and placing media spokespersons on major news and talk-show programs; and distributing press releases, clip art, and feature stories to local print media. In addition, the regional CIS network has engaged in more interpersonal outreach efforts based on NCI priorities, efforts that are directed toward their region and local communities. Specifically, this involves working with key community intermediary groups, who then carry the targeted message to their constituencies. In the past, this effort has been somewhat sporadic; however, since 1990 OCC has placed a higher priority on these efforts by creating a new staff position within each regional CIS office dedicated to outreach activities.

The decision to establish regional CIS offices was made by NCI with a great deal of forethought. Clearly, establishing one centralized telephone information office to serve the entire nation would be much easier to implement and manage on a day-to-day basis. One of the overriding considerations in favor of establishing a network of regional offices, however, was the high priority given to providing local referrals to CIS callers, a goal that can best be accomplished on a regional and local basis. Another key consideration, as noted above, was the decision to use the CIS network offices as regional outlets to coordinate and conduct community outreach programs, especially in concert with NCI-designated regional cancer centers. Prior to 1993, the regional CIS network provided telephone coverage to approximately 80% of the U.S. population, with the remaining 20% of the calls triaged to the national CIS office located in Maryland. This key policy decision to maintain a network of regional offices

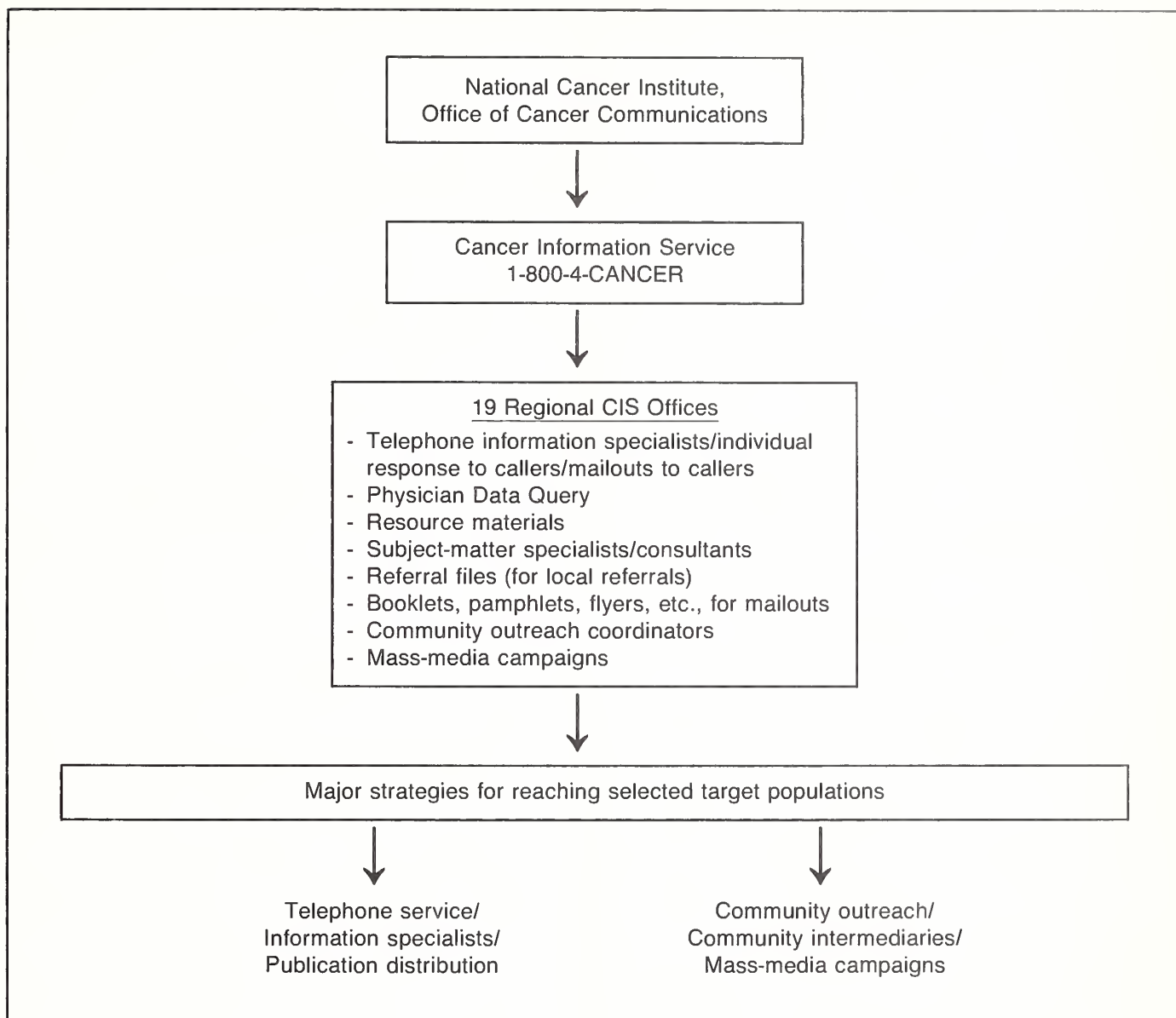


Fig. 1. Overview of the CIS network.

has been reaffirmed and extended in the most recent CIS contracts. As noted by Morra et al. (1) in this monograph, the 19 regional CIS offices began covering the *entire* U.S. population in 1993.

Given the decision to decentralize the dissemination of cancer information through the regional CIS network, quality control has remained a high priority at OCC. To ensure appropriate quality control, OCC has relied on five basic strategies:

- A rigorous training and continuing education program for CIS information specialists.
- Ongoing monitoring of live calls and review of CRFs by the CIS telephone supervisor and/or CIS project director within each office.

- An ongoing test-call system conducted by OCC to monitor the responses of CIS information specialists to specific caller requests.

- Submission of annual reports to OCC for programmatic review.

- Semiannual network meetings to provide feedback and direction to regional CIS staff on the functioning of the CIS.

ORGANIZATION OF THE MONOGRAPH

This monograph has been organized into three major sections.

The first section begins with a paper by Morra et al. (1) that provides a comprehensive overview of the history of

the CIS. Emerging from this paper is a clear description of the dynamic nature of the CIS as it has evolved and matured over the past 15 years. The second paper, by Arkin et al. (2), provides a comprehensive overview of the use of the mass media by the CIS. Two key observations from their analysis are the tremendous impact that mass-media campaigns have on CIS call volume and the need to coordinate such campaigns carefully with the regional network, which must respond to the substantial increase in requests for information generated by these campaigns. The third paper focuses on the community outreach programs and use of community intermediaries by the CIS. In this paper, Morra et al. (3) provide a brief history of the CIS outreach effort. They also highlight what would seem to be a new era in community outreach efforts by the CIS, with the addition of a new staff position, dedicated to community outreach efforts, within each regional CIS office. The final paper in this section describes a new test-call system that will be implemented by OCC for quality control and program evaluation. As described by Kessler et al. (4), the Cancer Information Service Telephone Evaluation and Reporting System (CISTERS) constitutes a significant upgrade of the previous test-call system used by OCC for quality control and training.

The second section is devoted to previous research involving the CIS. A central unifying theme of this part of the monograph is that the CIS has served as a significant laboratory for research on how to communicate cancer information to the U.S. public effectively. A corollary theme of this section is that there still remain significant untapped opportunities for additional research involving the CIS. This section begins with a paper by Marcus et al. (5), which provides a comprehensive overview of previous CIS-based research. Based on this literature review, the authors propose several lines of inquiry to guide future research efforts by the CIS.

The remaining papers in this section are linked to a special research initiative funded by NCI's Division of Cancer Prevention and Control (DCPC). In 1987, the DCPC created special set-aside funds to support "Cancer Communications Systems Research." Five studies were subsequently funded as part of this initiative, all of which focused on the CIS. The five remaining papers in this section present the final results from this program of research. The paper by Freimuth (6) examines a gap in CIS utilization and cancer knowledge between Whites and African Americans. Freimuth documents underutilization of the CIS by African Americans and notes that African Americans who call the CIS are similar in educational attainment to Whites who call. Freimuth also documents an educational gradient in cancer knowledge and practices among African Americans and notes that television may be the preferred channel for the CIS to reach African Americans.

Manfredi et al. (7) report the results of a unique study examining cancer patients who called the CIS. Among the numerous findings from this analysis was the indication that patients will share the information they obtain from

the CIS with their physicians, thus raising the intriguing possibility that the CIS may indeed influence clinical decisions regarding cancer treatment. These investigators also report that cancer patients who called the CIS were highly satisfied with the service they received.

The last three papers in the second section report results from randomized controlled trials that were designed to test various cancer-control interventions within the CIS, including a smoking-cessation program that targeted blue-collar workers (8); a mass-media campaign that utilized paid advertising to target women cigarette smokers who have young children (9); and, finally, a proactive counseling protocol that was designed to promote screening mammography among age-eligible female callers to the CIS (10). Taken together, this body of research provides a compelling precedent for continued funding of special research initiatives that focus on the CIS, especially research that uses the CIS as a major service-delivery component in cancer-prevention and control-intervention trials.

All of the papers contained in the first two sections of the monograph were part of the original concept paper prepared by the editors. One of the distinguishing characteristics of this monograph is that regional CIS staff members not only were involved in the planning of the monograph but also served as contributing authors on virtually all of the papers. In a very real sense, this monograph is the product of the regional CIS network and, thus, serves as a tribute to the leadership and commitment of the regional CIS staff that make this network function on a day-to-day basis.

The involvement of the regional CIS network in the preparation of this monograph is especially evident in the third section. *All* of these papers were originally suggested and conceptualized by regional CIS staff. Thus, included in this section are papers dealing with such timely and important issues as the interface between the CIS and NCI-sponsored clinical trials (11,12); the use of the CIS by minority populations (13); CIS outreach programs designed to reach populations of low literacy (14); the role of the CIS in targeting older populations (15); and future opportunities for computerization within the CIS (16). Finally, the editors of the monograph inherited the formidable task of trying to synthesize some of the lessons learned over the past 15 years. Morra et al. (17) embrace this challenge in the last paper of the monograph.

CONCLUDING REMARKS

Ultimately, it will be left to the readers of this monograph to decide for themselves whether we have achieved the major objectives that guided its development. Perhaps 15 years from now, NCI will publish a second monograph to mark the 30-year anniversary of the CIS. Given the dynamic evolution of the CIS over the past 15 years and the virtual explosion in information-processing and information-dissemination technology, it is difficult to imagine what the CIS will look like in the year 2005.

However, one observation can be made with absolute certainty: if the legacy of the CIS is carried forward to a new generation of Americans, our children and grandchildren will be the beneficiaries of this truly remarkable public service program sponsored by NCI.

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History of the Cancer Information Service

Marion E. Morra, J. Paul Van Nevel, Eleanor O'D. Nealon, Kate Duffy Mazan, Chris Thomsen*

The Cancer Information Service (CIS) was established on July 1, 1975, following the mandate of the National Cancer Act of 1971 giving the National Cancer Institute (NCI) new responsibilities for educating the public, patients, and health professionals. Funded under a contract mechanism, the CIS has become one of the longest-running community programs in NCI. The CIS has been able to set up and maintain high-quality service, giving accurate, up-to-date medical information to cancer patients and their families and friends, to health professionals, and to the general public. The CIS network, which has taken more than 5 million calls since its inception, has weathered many changes, both at the national and the local level. Its current call volume, in excess of 500 000 calls per year, makes it one of the most heavily utilized health-related telephone helplines in the country. Using a standardized Call Record Form, data on calls have been recorded consistently since 1983; the dataset now contains information on more than 4.2 million calls. An outreach component that acts as NCI's field arm has been part of the CIS since its inception. The CIS has matured into a stable system that has been reconfigured into 19 regional offices, covering the entire country. These offices run the telephone service and serve as NCI's outreach arm, working with intermediaries to carry out NCI information and education programs in local communities. [Monogr Natl Cancer Inst 14:7-33, 1993]

"I want to thank you for all the help, support, care, and information I have received. I am so scared, and I know I have called . . . at least a dozen times. I can never repay you for your kindness."—Barbara, Florida

"Beginning with the first voice on the phone, I felt someone cared."—Sheila, California

In the 15-year history of the Cancer Information Service (CIS), the milestones have been significant and the statistics have been impressive. Yet, it is easy enough when describing the history and accomplishments of the CIS to lose sight of the enormous impact the program has on the individual caller: one phone call, one conversation, can save a life. This is the true essence of the service and the most rewarding aspect of the program.

When the fledgling CIS began its life on July 1, 1975, Frank J. Rauscher, Jr., Ph.D., the director of the National Cancer Institute (NCI), called it "an effort to make existing and new knowledge available throughout the nation" (1). The early architects of the CIS faced enormous challenges in fashioning a mechanism that could present complex and diverse information accurately and

compassionately to a wide variety of callers—challenges that have been successfully met. The CIS has proven that a high-quality service can be established, maintained, and continually improved.

Today the CIS is a strong network of 19 regional offices, staffed with skilled health-information specialists. Working with standardized policies and procedures, the network gives up-to-date, accurate information on cancer prevention, detection, diagnosis, treatment, and rehabilitation to more than 500 000 callers a year. Standard data, collected on each call and synthesized nationally, constitute one of the largest, consistent, health-related datasets in the country. The CIS maintains resource directories of cancer-related services; develops and implements mass-media campaigns; and distributes a wide variety of NCI-developed printed materials and publications to the general public, to patients and their friends and families, and to health professionals. The CIS also includes an outreach arm, working with intermediaries to bring NCI programs and messages to local communities throughout the United States.

This paper will trace the history of the CIS from its inception to its most recent reconfiguration. It will cover the most critical issues the network has faced, its accomplishments, as well as the obstacles it has overcome as it has matured into the sophisticated communications system it is today. Three time periods will be examined: the beginning years of the 1970s, the growth years of the 1980s, and the expansion years of the 1990s.

THE BEGINNING YEARS—THE 1970s

The genesis of the CIS can be found in the National Cancer Act of 1971 (2), which began a revolution in the programs of NCI. As the first of the categorical institutes that now constitute the National Institutes of Health, NCI was created in 1937 to conduct and support cancer research. The 1971 act, which intensified and expanded the research program, gave NCI new responsibilities to ensure that research findings would not lie fallow on a shelf but would be made available quickly for use by health professionals, patients, and the public.

The 1971 act mandated additional initiatives including a cancer-control program to emphasize prevention, early detection, rehabilitation, and patient/physician access to the latest cancer treatments; communications programs to

*See "Notes" section following "References."

educate the public, patients, and health professionals; and the creation of a geographically balanced network of "national research and demonstration centers," now called comprehensive cancer centers. In terms of information programs, the act directed NCI to "collect, analyze, and disseminate all data useful in the prevention, diagnosis, and treatment of cancer" (2).

The 1974 amendments to the act (3) made the mandate stronger, directing that NCI "provide and contract for a program to disseminate and interpret, on a current basis, for practitioners and other health professionals, scientists, and the general public, scientific and other information respecting the cause, prevention, diagnosis, and treatment of cancer."

Throughout 1972 and 1973, NCI staff, with the help of cancer experts from around the world, engaged in massive planning efforts to devise ways of implementing the 1971 act. The result, called the National Cancer Plan, outlined goals, strategies, and approaches across the spectrum of cancer research and control. As a part of this effort, the CIS was conceived in late 1973 as a way of giving cancer patients and members of the public immediate access to the latest information on cancer.

Access to the "Best" Care

The driving force behind the creation of the CIS was the perceived need to help cancer patients obtain the best care. Earlier that year, the son of Massachusetts Sen. Edward M. Kennedy had been diagnosed with a sarcoma. Because the family knew how to work within the cancer establishment, it was able to obtain the most up-to-date, lifesaving treatment for a cancer that was then, in most treatment settings, largely incurable. NCI staff, working to devise better communications and education programs, were struck by the fact that the average citizen did not have the same access to the latest cancer information. They believed everyone should have equal access and that it should be easy to obtain and free. The concept of what is now the CIS was born.

An early champion of the new communications program was Mary Woodard Lasker, president of the Albert and Mary Lasker Foundation and one of the individuals most responsible for passage of the National Cancer Act. She wrote NCI's deputy director in December 1973:

I am hoping that a good cancer information center gets started that will not only help thousands of cancer patients but the general practitioners as well. Most of these doctors don't know anything about the new methods of treating patients, and an NCI information center would be able to advise on the right places and specialists to go to, to get help. . . . I am sure that you . . . will get something started in this country to help the millions of people who are afflicted with this disease (4).

Locating at Comprehensive Cancer Centers

In the beginning, planning for the CIS was wed to planning for the development of the nationwide network

of comprehensive cancer centers. These centers, many of which were identified and recognized in 1973, were given specific responsibilities by the National Cancer Advisory Board (NCAB) to conduct outreach and education programs for their regions. NCI reasoned that a regionally operated, nationally controlled CIS would help centers fulfill their outreach responsibilities; provide centrally developed, up-to-date information; and give all citizens information and local resources.

At NCI, the Office of Cancer Communications (OCC), the Division of Cancer Control and Rehabilitation (DCCR), and the Cancer Centers Branch began collaborating to develop what was then called the Comprehensive Cancer Centers Communications Network. With active support from the Cancer Centers Branch and staffing largely from OCC, NCI decided to fund the network from DCCR (or cancer-control) funds. That division's budget was rising rapidly in the early 1970s, and it needed good ideas to support.

OCC staff presented the concept to a gathering of comprehensive cancer center directors at a meeting held in May 1974 (5). The center directors, who were more interested in other matters, did not oppose the idea (6).

As a further check on the concept, NCI staff visited the Memorial Sloan-Kettering Cancer Center, Roswell Park Memorial Institute, the University of Texas System Cancer Center, and Wisconsin Clinical Cancer Center, all of which were operating various types of telephone systems to provide access to cancer information. The trips revealed that to implement the Comprehensive Cancer Centers Communications Network, centers would need support defining target populations, building reference systems, fashioning media and marketing campaigns, managing the service, and coordinating intercenter relations (7).

In addition, NCI staff made test calls to comprehensive cancer centers and to American Cancer Society (ACS) divisions in the centers' regions. Those calls indicated that the public had great difficulty getting information about cancer experts and institutions (7).

First Request for Proposals

In September 1974, NCI issued a Request for Proposals (RFP) to operate network communications offices; the RFP limited competition to comprehensive centers (8). The RFP, referencing the National Cancer Plan, announced that

funds will be available through contracts to support the core staff of information/education offices and to finance development of the minimal materials and resources required to conduct the offices' activities. . . . The contractor shall establish a communications office, or other focal point, for providing the services listed below, as well as for planning additional education and information programs. . . . The Communications Office shall establish and make known a two-way service, such as a toll-free number, providing cancer information to both the public and health professionals. . . .

The RFP also directed the bidders to maintain up-to-date information about “National, regional, state, and local programs, services, agencies, organizations, and health institutions concerned with cancer.” In addition, they were to maintain the latest information on all aspects of cancer and information about “professionals available for consultation on specific areas of expertise in the center, the community, the region, and at NCI.”

Awards to comprehensive cancer centers. By July 1975, NCI had completed contract negotiations and made 17 awards, one to each of the comprehensive cancer centers. In a letter to center directors in July 1975, Rauscher pointed out that

this communications network is one way that NCI is meeting the new legislative obligation to provide more information about cancer to health professionals and the public. It is clear that the intent of Congress was not to establish a massive public relations program. Since this program is truly intended to be a public service, we all must constantly guard not only against use of the individual offices and the entire network for public relations purposes but against even the appearance of such use.

He also pointed out in the letter that the network represented “one of the first nationwide programs to be anchored by the centers . . . and it will have a powerful effect in establishing the credibility of the comprehensive cancer centers and of the National Cancer Program.” He added that NCI staff were ready to give all the help the centers needed (1).

National office contract. Because the cancer centers served only a portion of the country and because NCI wanted the entire nation covered by the telephone system, NCI also issued a request for contract proposals for the operation of a “national” office. NCI intended for the national CIS office to take calls from parts of the country not having cancer center coverage. The national CIS office would be open 24 hours a day, 7 days a week and include a warehouse that would distribute NCI publications to the public and to CIS offices (9).

The contract for the national office was won in 1975 by Biospherics, Inc., a contractor in Maryland, which has recompeted for the contract successfully ever since; service began in April 1976. The national office received 3000 calls on two telephone lines the first year. By 1979, the office was taking nearly 24 000 calls a year on four lines. Because almost no one called in the middle of the night, service was cut back in 1979 to 16 hours a day—8 AM to midnight, Eastern time.

Although the concept for the CIS was a simple one, its implementation would be challenged in the early years by many issues, such as lack of agreement on what was up-to-date information, and local medical politics that in several regions prevented referrals to physicians or institutions where the latest treatments could be obtained.

The American Cancer Society's Role

In 1973 and 1974, the leadership of NCI and ACS held a series of retreats in Anneville, Pennsylvania. The retreats, called by ACS, were a two-way information vehicle, informing top NCI staff about ACS programs and capabilities and providing ACS with information about plans for new NCI control programs before those plans were final.

ACS viewed NCI's new control mandate with some ambivalence. On the one hand, more cancer control could be mounted with an infusion of tax dollars. On the other hand, the new federal control efforts could undercut ACS's role and visibility in the community and, ultimately, cause loss of financial support. In addition, because of the history of other federal programs, ACS staff worried that NCI would drop new programs into the field and then, when priorities changed, abandon them and leave ACS “holding the bag.”

ACS worked to help NCI develop needed programs that would not interfere with its own activities. Regarding the development of the Comprehensive Cancer Centers Communications Network, ACS recognized that the public perceived ACS as an up-to-date source of information, yet knew that callers to its local offices often were handled by volunteers untrained and unequipped to provide the complex information that callers needed. In addition, because ACS was strongly influenced in many aspects by practicing physicians, it was not able to venture into the political minefield of second opinions and physician referrals in any meaningful way.

ACS decided to work with NCI and, through its divisions, with the centers to develop the communications network. Its participation (and monumental political clout) gave it an element of control and ensured that it would have visibility related to the new service, which all expected to become highly popular.

Dilemmas for the Cancer Centers

The center directors were perplexed by some of the requirements NCI was imposing on the network. They, too, were troubled about the medical-political minefield of second opinions and physician referrals. After all, they depended on good relationships with physicians in their communities for patient referrals to their centers, and most could think of no quicker way to damage those relationships than to single out “experts” for second opinions or other referrals.

In addition, most of the new comprehensive cancer centers had been created at academic medical centers, and their very creation had been controversial among the faculties and administrations of their own institutions. For a center to be recognized, NCI required the center to have a freestanding identity and its director to have authority equivalent to a department chairperson. In other words, the creation of a center in an academic medical institution required other faculty and established departments to give up elements of control, authority, and responsibility.

The new network would also create another “voice” speaking to the public from within the parent institution and another problem for its administration. Since the CIS was a service program, rather than a research one, it was also an anomaly in most academic settings.

Forging the Alliance

In the spring of 1974, a small group of cancer communicators representing NCI, ACS and some of its divisions, and a few cancer centers met in Chicago to discuss the problem of relationships among the different organizations. By then, the issue was not whether to have a Comprehensive Cancer Centers Communications Network but rather how to overcome the political problems and put it in place. The representatives decided that a major problem was communications among the groups.

In addition, there was an impression, probably correct, on the part of ACS divisions and the cancer centers, that an important, politically sensitive program was being developed outside their control. They were worried that this program would be thrust upon them and that they would have to deal with the aftermath. Although at the national level NCI and ACS were reaching an accommodation, tenuous as it was, there was misunderstanding in the field; there were feelings of uneasiness and apprehension between some cancer centers and ACS divisions. As a result, the Chicago group developed a plan to convene all of the parties on a periodic basis. The intent was to inform everyone of the concept for the network, what it might actually do in practice, collectively identify problems it might create—particularly at the cancer center and ACS division level—and devise ways to overcome those problems.

Two upcoming events provided an opportunity. NCI and ACS had planned for some time to cosponsor two major national conferences on advances in cancer management, one to be held in November 1974, the other in April 1975. The Chicago group decided to attach to each of these conferences a Public Information Workshop. These workshops were the first of what became known as National Cancer Communications Conferences. Both conferences, the first in New York and the second in Denver, brought together NCI staff, public-affairs officers from the cancer centers’ parent institutions (most centers did not have their communications staff yet), representatives of the national ACS, and individuals from ACS divisions in the cancer centers’ regions. By the time of the Denver conference, some of the centers had hired communications staff, who joined the larger group.

The first conference’s program was basic: the roles of NCI and ACS and the need to inform the public about cancer (10). The second conference became much more specific about how groups could work together on developing the new network. In addition to general sessions, participants divided up by region to address problems and opportunities specific to them.

A third conference was held in Houston in October 1975. By this time, the first CIS contracts had been awarded and the cancer centers had hired the personnel to

run the network offices. This new staff joined the regular group from NCI, ACS national and division offices, and cancer centers public-affairs staff. The objectives of these meetings were to provide the opportunity for the give and take between the organizations, to ease concerns, and to build cooperative undertakings.

During 1976, NCI and ACS sponsored a series of regional communications conferences, rather than national conferences, to allow those most involved with particular services to concentrate on issues specific to their regions. The Fourth National Cancer Communications Conference, held in Chicago in 1977, was more general in nature. The network no longer was the major issue; this conference was designed to keep ACS, NCI, and cancer centers staff up-to-date on the latest developments in cancer research, introduce them to new health-communications techniques, and foster cooperation across a broader scope of communications programs.

This tradition of National Cancer Communications Conferences, begun in 1974, provided an important forum for communications that has continued. The conferences have evolved into major events, offering preconvention training opportunities along with major conference sessions and a myriad of workshops on communications issues. The fifth conference was held in February 1984 and the sixth in January 1990; both produced written proceedings (11,12).

Relationships Between NCI and its Communications Contractors

In Houston in 1975, NCI scheduled a meeting of the network contractors immediately following the larger communications conference. New staff from NCI’s DCCR, which was footing the bill, came to the meeting prepared to dictate to the contractors how they should perform their duties (13). As some of the NCI staff, disregarding the collegial nature of the enterprise and ignoring all the careful groundwork that had been laid, began laying down laws, regulations, and rules, the new contractors—who were academics at heart and by experience—erupted in anger. Later, the new cancer centers communications staff met privately to develop a list of demands regarding administration of the program (14).

The crisis ultimately resulted in a new relationship between NCI and its communications contractors. Unlike other contractors, those in the network would be subject to less “policy” direction on many matters and given leeway to develop the CIS to best fit within the cultures of the individual centers and the broad community each served. In fact, cancer centers were allowed leeway on how they would develop procedures for second opinions and physician referrals. They were even allowed to develop answers to callers’ questions on matters of medical practice and science. For example, a question on breast cancer screening with mammography, an area of great controversy in the 1970s, found some centers answering in a way that reflected the opinion of its scientific staff, rather than NCI’s opinion.

Choosing a name. The issue of a new name for the network also came up at the contractors' meeting. The term "Comprehensive Cancer Centers Communications Network" was too cumbersome to use with the public. Earlier in 1975, OCC staff had announced at a meeting of the NCAB that the network would be called "Cancerline," only to have NCI's Associate Director for International Affairs (who ran the International Cancer Research Data Bank) object. He had just named his big database at the National Library of Medicine "Cancerline" and did not want OCC to use it. So, before the Houston meeting, NCI decided to call the network "Controline." Beautiful graphics were prepared, registration materials in Houston were handed out in vinyl bags silk-screened with "Controline," and the new name was displayed everywhere.

Representatives of the cancer centers rejected the name, feeling that it did not reflect the nature of the service accurately. They came up with five alternative names (Cancer Information, Cancer Information Network, Cancer Information Service, Cancer Questline, and Cancer Answers) and stated that any of them, or other alternatives starting with the word cancer, would be acceptable, providing that NCI would test consumer and medical reaction (14). NCI felt there was not enough time to conduct a market test, so it polled the contractors and accepted the top choice. The network became the Cancer Information Service—and the vinyl bags became collector's items.

The contractors' meeting in Houston was important in establishing a partnership between NCI and the contractors on a host of matters. At that meeting, a system with five task forces—evaluation, management, linkages with other institutions, telephone operations (which included training), and promotion and publicity—was established. The system of task forces that gave cancer center communications staff a major role in developing management and operational tools (15) has served the network well. The use of task forces with network representation continues today.

Development of policies. Although the contracts were in place by mid-1975, the centers needed to prepare to open the service. Major tasks were accomplished in a short period: resource directories were developed, the telephone system was set up, a promotion plan to let the public know about the service was developed, staff was hired, and volunteers were recruited. (The original contracts mandated the use of trained volunteers to answer the telephones—a requirement that continued until the late 1980s.)

NCI ran two training workshops for the NCI and ACS teams to assist the new offices in readying the volunteer information specialists to answer the calls. Following the recommendations of the Telephone Operations Task Force, the telephone supervisors and their ACS counterparts were taught to train the volunteer staff. Along with several modules that focused on cancer (such as basic anatomy and physiology, definitions, and sites and types of cancer), the training contained components on the recruitment, selection, and management of volunteers; on attitudes toward cancer; on cancer myths; and on the legal aspects of referral operations (16).

In an April 1976 memorandum to management, NCI's newly appointed co-project-officers, Elaine Bratic and Warren Dunn (Table 1), outlined the minimum necessary features of the communications program (17):

1) Installation of a toll-free telephone service. "We can expect quick compliance with contract terms in some locations; in others we recognize the necessity of moving more slowly. We should be flexible in time requirements as long as there is evidence that the Center is making progress."

2) Promotion. "Intensive promotion directed to both the general public and to those audiences at highest risk will help assure that the [telephone service] is used. . . ."

3) Public education. "To take advantage of the telephone mechanism, the contract requires that communication offices engage in appropriate public education/information activities. While we have not finally defined what is meant by 'appropriate' activities, we mean generally those kinds of activities which: plug the gaps in current service to the public; utilize the telephone service in some way; and are aimed at hard-to-reach, high-risk audiences. . . . Within limitations placed on funding, the communications office will be unable to undertake more than planning activities. . . . we recommend that each Center provide us with evidence that they are engaged in planning public information and education programs aimed at specific audiences."

4) Physician referral. "This is one of the most important services of the communications program and one of the principal reasons for the program. We understand the delicacy of the issue, and we are not requiring that Centers actually make physician referrals at this time. However, we feel that Centers should at least initiate inquiries and raise the issue of physician referrals with appropriate people in order to lead to improvements in the current system."

5) Establishing and maintaining contacts with cancer-related and cancer-concerned organizations. "This project should be one in which any cancer-concerned organization feels welcome to participate, cooperate, and contribute."

6) Evaluation. "Common reporting forms have been developed for use by the network offices. . . . There are elements of the program which can be compared and should be, so that the best methods can be replicated by other programs."

The main elements of this memorandum were also communicated to the contractors. It was one of the first in a series of memos that established policy for the network (18). Because the CIS had no history, no tradition, and no

Table 1. CIS project officers

1975	Elaine Bratic
1975-1976	Elaine Bratic and Warren Dunn
1976-1978	Warren Dunn
1978-1979	Carl Larsen
1979-1980	Carlos Caban
1980-1982	Tom Kean
1982-1987	Judith Stein
1987-Present	Kate Duffy Mazan

standard practices and because everything was new and original, the project officers were often in the position of making specific operational policies on the run. To communicate policy as it developed and to ensure some consistency across the 17-office network, the project officers developed a system of circular memos, ultimately numbering more than 400, that informed the network of new policies, procedures, and requirements. The memos ranged from information on how to handle calls about donations to information about when quarterly reports would be due and everything in between.

Opening for Business

The first "official" CIS calls were taken in February 1976 in Florida, which began limited service in Lee County and expanded to other southern Florida counties in the spring (19). Each month, one or more of the offices opened their phone lines, and by mid-1976, many of the 17 offices had opened either statewide or on a pilot basis in small areas. By September, 13 were operational, each with its own toll-free 800 telephone number. By the end of 1976, the entire system had received 47 000 calls.

The communications service in Florida was billed as a service of "the Comprehensive Cancer Center of the University of Miami, the National Cancer Institute, and the American Cancer Society." This billing, as a project of multiple institutions, including ACS, was imitated by most CIS offices as they opened. It was an important concession to ACS, allowing it to maintain community visibility while diminishing the visibility NCI could have had if it had promoted itself as the sole supporter of the CIS. As the new service opened, relationships with ACS divisions varied. At one extreme was a CIS operated out of an ACS office; at the other extreme was a relationship fraught with competitive feelings.

Communications With the Network

It was obvious from the beginning that a telephone service designed to answer cancer questions had to stay current not only with new scientific findings but also with local and national events that would cause the public to call. NCI, as a national organization, was more able than individual centers to monitor scientific developments and public events about which the public would want information, and it sought to devise ways to communicate rapidly with all of the offices. In the mid-1970s, there was no express mail service, no sophisticated fax system, and no electronic mail capability.

Weekly packages. As a way of keeping centers up to date, NCI began sending a "Weekly Package." This routine mailing, which has continued throughout the history of the network, not only included information about scientific developments and warned of impending news events that could trigger calls but also was a way to distribute new educational materials developed by NCI or a center.

Even before the network was fully operational, NCI was considering the purchase of telecopiers—primitive fax

machines—for the network offices (20). NCI believed that the existence of a toll-free telephone line inherently generated an expectation of on-the-spot answers. Ultimately, telecopiers were purchased and supplied to the network. Unfortunately, they were so slow and difficult to use that it could take all day to transmit a long document to each of the 17 offices. The machines fell into disuse, and until more modern technologies were developed, NCI staff manned phone banks to call each office when something urgent needed to be communicated.

Semiannual meetings. NCI wisely had planned for semiannual meetings of network staff, not only to discuss business matters related to the contracts but also to communicate about major issues faced by the network and to plan for overall administration of the program. After the Houston meeting, NCI added funds for the task forces to gather prior to the meetings. The semiannual meetings of the communications staff allowed for discussing problems and provided a structure for forging solutions that all could live with. Although stormy at times and difficult for NCI to control, the semiannual get-togethers solidified the feeling of network, as individuals from around the country worked in teams with the NCI staff to solve common problems in carrying out the difficult tasks embodied in the contract. These meetings, which have now grown to a total of 30, continue today; they have been a major force in keeping the network strong and vibrant and making it a living entity.

Three issues have posed major dilemmas for the CIS from its origin: evaluation, publicity and promotion, and outreach. All were a part of early discussions in the network; all have achieved major successes and have continued to be major activities in the network.

Evaluation of the Service

The first concerted efforts at developing an evaluation plan for the network began in late 1975, with the creation of an Evaluation Task Force, consisting of three network representatives, the NCI co-project-officers, and a key staff representative of an NCI support contractor (15). At the March 1976 network meeting in Miami, this task force presented its proposal for a common data-collection form for recording inquiries, a proposed survey of CIS users to measure callers' satisfaction with the service, objectives and measures for evaluating programs aimed at the public and health professionals, and a set of technical materials to assist the network offices in understanding and implementing the evaluation process (21).

After considerable discussion, CIS program staff agreed that the evaluation plans were too ambitious. The core of the problem, which would take years to solve, was how to fund evaluation activities.

The evaluation components proposed by the individual institutions as part of their original CIS contracts were not funded by NCI. The "deliverable" was left in the contract, however, with the promise that separate funding mechanisms would be available. At the first network meeting, NCI stated that it would help "construct evaluation methodologies and instruments and assist in data

collection” (22). By August 1976, NCI’s position was that it “would consider the evaluation obligation met if Coordinators submitted monthly summaries of statistics related to the telephone operation—process evaluation. . . . DCCR would not require a sophisticated effort be made to determine the impact of the program on target audiences” (23).

Origin of the dataset. As the services became operational during the last half of 1976, NCI and the CIS offices were faced with a definite need to implement an evaluation system with few local resources and with little hope that national resources would become available on a timely basis. At the New Orleans meeting in November 1976, all centers agreed to use the same form for recording a minimum set of information on all calls. Five offices also agreed to pretest this Call Record Form.

By early 1977, a “uniform reporting structure” that all offices would use for NCI quarterly reports was agreed upon, consisting of the number of requests during the reporting period by mode, type of user, type of questions asked, and site or type of cancer involved; standardized definitions to promote uniformity in coding the data were also adopted (24).

Although this reporting system became operational, there was no provision for checking the uniformity of the data reported and the degree to which the various CIS offices were adhering to the reporting requirements. The result was the existence of 17 individual programs, each different from the others in terms of depth and quality of information being gathered; however, this early uniform reporting structure was an important building block for the database that today contains information on over 4 million calls.

User survey. At the Miami meeting in 1976, the CIS offices agreed to implement a second recommendation of the Evaluation Task Force, the user survey. The survey consisted of a mailback questionnaire with a minimum set of questions to be sent out locally rather than from a central source. Five offices also offered to pretest the user survey (25).

Although it was not a contract requirement, 12 contractors consistently conducted user surveys locally for several years—providing an essential early barometer for judging the quality of the service from the users’ point of view. A 1979 review found two major problems with the survey data. First there was no uniform dataset. The data from the individual surveys were not comparable because, although similar questions had been asked, the wording of the questions had changed over time. As new CIS offices opened and as personnel changed, new surveys were developed. By 1979, many offices were unaware of the baseline questions agreed upon in 1976. The second problem was that the methodologies differed. Some chose to send questionnaires to all callers. Others surveyed all callers to whom information had been mailed. Some offices sent reminders to boost response rates. Others used postage-paid forms.

The report examining the user survey data concluded:

Unless specifically worded questions asked to uniformly selected audiences are mandated by NCI, the individual CIS offices will undoubtedly continue to use individually developed and individually worded user satisfaction forms to fulfill their individual needs with no nationally applicable information available (26).

Publicity and Promotion

Publicity and promotion was also the topic for an early task force. Among the first five task forces appointed late in 1975, it was composed of network representatives, the NCI co-project-officers, and OCC staff. The Publicity and Promotion Task Force produced working documents that evolved into a national media plan for the CIS (27). The plan, outlining tasks to be performed by and for the network, was approved by each of the cancer center directors and appropriate staff.

The plan gave the primary responsibility for publicity and promotion activities to the local CIS offices. NCI would assist the network by providing nationally produced materials to augment local publicity and promotion efforts, ensuring proper coordination and sharing of network-produced materials and ensuring that adequate policies and guidance were given to network offices conducting and staffing meetings of the task force. It was agreed that NCI would take the lead in initiating promotion of the CIS to the national media, using the local 800 telephone numbers. All nationally produced materials would also feature the local 800 telephone numbers.

Early Outreach Activities

There was from the beginning, on the part of NCI, an interest in seeing the telephone service and the other components of the CIS develop in a parallel and complementary fashion. The 1975 contracts included limited funding to undertake outreach activities. In the early years, however, the task of setting up and operating the telephone service took almost all the time and energy available, at both the local and national levels.

In addition, it was difficult to determine what outreach activities should be part of the program. The original guidelines for the CIS issued by NCI in 1976 stated:

The Network offices shall support existing public and professional information and education programs within their area of service to further the reach and increase the impact of those programs. A public and professional education committee consisting of NCI, ACS, and Center personnel has been established to identify gaps in existing information/education activities. Highest priority shall be attached to assisting in the establishment of programs which reach professional and public audiences not currently benefitting from existing programs. Those audiences must be identified and reached in cooperation with the ACS and other cancer-concerned organizations and institutions (28).

At each network meeting, two or three of the education/outreach programs being carried out at the local level would be highlighted. OCC representatives would also present national initiatives and opportunities for joint work on these programs with the local offices. There was no mechanism, however, for making a national team effort out of the OCC initiatives, since local offices were able to choose which programs they would pursue. It would take years before the outreach component of the program would take a form that could make it an equal partner with other elements of the CIS network.

First Recompetition

By 1977, when DCCR reviewed, for its Board of Scientific Counselors, the top divisional priorities for fiscal year 1978, it included the CIS. Its report said the CIS would

create and/or maintain a comprehensive listing of cancer-related resources and services in their area of service; recruit and train volunteers to provide information about cancer to users of the toll-free service; develop and implement cancer education for special target audiences at higher risk; and help centers reach out to community physicians (29).

In the summer of 1978, the network's project officer reported to the DCCR board that the first network recompetition for the second series of 3-year contracts had been completed (30). The merit reviewers identified several strengths of the program: development of such a large-scale social action program in such a short period of time; establishment of the necessary linkages among the ACS, other voluntary cancer-related agencies, a number of health-care resources, and the various centers themselves; recruitment of volunteers and completion of a training and management program for them; development of a sense of network among the contractors; resource support obtained from a variety of sources; and development and implementation of the toll-free telephone system.

They also found major weaknesses: lack of emphasis on prevention and rehabilitation intervention areas, limited evaluation of the program, limited educational program development directed toward allied health professionals and high-risk minority audiences, and an unevenness in the quality of the service, with some centers performing much better than others.

New centers added. The project officer noted that in this second round of contracts, 15 of the original centers had had their contracts renewed and contracts also were awarded for the first time to new comprehensive cancer centers at Ohio State University and the University of California at Los Angeles (UCLA). Several of the offices were now covering more than their own states. Twenty states, in which more than half the U.S. population resided, were covered by network offices, and plans continued to add new territory to the network in an orderly way.

Two centers, the University of Alabama and the Colorado Regional Cancer Center, were not renewed. The DCCR board was told that the merit reviewers were concerned that Alabama had not established the telephone service because the Alabama State Medical Association, fearing the telephone service would lead to disruption of referral patterns, withheld its cooperation. The merit reviewers found that Colorado had not paid much attention to professional and public education but instead was using the program as a public-relations effort.

Addressing the evaluation weakness. The new 3-year contracts offered an opportunity to address the evaluation weakness found by the merit reviewers. NCI required the CIS offices to submit local evaluation plans, which were reviewed by an ad hoc committee of evaluation consultants. Each plan was assigned a score based on its degree of compliance with a set of criteria developed by the ad hoc committee. Unfortunately, these criteria were not provided to the contractors prior to the submission of their plans, and thus the plans submitted covered a wide range of formats and content. Although the results of the committee review were discussed at the network meeting in Maryland in May 1979, no qualitative feedback or diagnostic results of this review were ever provided to the individual network offices nor were the offices encouraged to implement the plans (31).

At the 1979 Maryland meeting, however, various local CIS representatives initiated development of a dataset that would provide a national picture of the types of inquiries being answered by the CIS offices. Representatives from two of the CIS offices accepted responsibility for obtaining data for a specified period from each of the network offices, collating the data, resolving tabulation discrepancies, providing a national analysis, and distributing these data to the network. This effort brought forth the following summary of CIS evaluation efforts:

Resources allocated for evaluation at both the individual network communications office and national levels have been extremely limited. The large majority of substantive evaluation results for the network has come from the efforts expended by the individual network offices. Despite numerous attempts made at national evaluation of the telephone information service, there is today no carefully designed, integrated, coordinated, and reliable evaluation program (31).

As the decade came to a close, it was clear that the CIS had made great strides in fulfilling the vision of its founders (Table 2). A nationwide system had been established in a short time. Up-to-date cancer information was being provided over the telephone, with many of the local offices also working on useful outreach programs. A major promotional effort had been developed. A strong system of task forces, with both local and national representatives, governed the system. The CIS had met the challenges of its infancy. It needed to continue developing both in breadth and in strength.

Table 2. Chronology of CIS events—the 1970s

December 1971	National Cancer Act signed into law
June 1974	National Cancer Act amended
September 1974	Original solicitation for proposals to begin CIS program issued by Communications Branch of DCCR
November 1974	First National ACS–NCI Cancer Communications Conference, New York City
April 1975	Second National ACS–NCI Cancer Communications Conference, University of Colorado
July 1975	First 17 CIS contracts awarded to NCI-designated comprehensive cancer centers
October 1975	Third National ACS–NCI Cancer Communications Conference, Houston
October 1975	First task forces appointed
December 1975	First training session held for the CIS and ACS partners
January 1976	First local outreach program launched
February 1976	First CIS telephone calls taken (Florida)
March 1976	First local user survey mailed
April 1976	National CIS office began service
May 1976	First CIS network television and radio spots aired
November 1976	Call Record Form introduced
February 1977	Uniform reporting structure operational
April 1977	National Media Plan for the CIS implemented
June 1977	Fourth National ACS–NCI Communications Conference, Chicago
January 1978	Promotion campaign targeting African Americans launched
February 1978	First CIS network television spots in Spanish aired
April 1978	NCI Asbestos Awareness Campaign launched
August 1978	Second set of 17 CIS contracts awarded

THE GROWTH YEARS—THE 1980s

The 1980s brought major changes to the CIS. The program matured and took advantage of new technologies. As local offices gained experience, their quality, uniformity, and impact grew. The work of the entire program—from training to evaluation, from quality control to promotion, and from publicity to outreach—was affected. This was a period of rapid growth, with the network's services expanding and the sophistication of the callers continually increasing.

During this time, a fundamental shift in power took place. The network received more national direction, and local offices lost much of their autonomy. The shift occurred for a number of reasons.

- First, the CIS was costing NCI large sums and Cancer Institute advisors were demanding either that the service be of high quality or that the funds be diverted to other, perhaps more worthy, projects.
- Second, private individuals were testing the system and finding some areas that could be improved upon. Rose Kushner, a nationally known advocate for breast-cancer patients, made test calls to each office in 1978 to see how they performed. Breast cancer, at that time, was a topic laden with medical controversies, ranging from the radiation risk of mammography to the use of new diagnostic tests, such as the estrogen receptor assay. It was the very topic on which local CIS offices had the most local leeway in developing responses. Kushner did not like the answers from some offices, and she pursued the issue at NCI and in Congress, creating political pressure to exert more control over the CIS network.
- Third, those operating the program at NCI began conducting test calls themselves and immediately saw firsthand the need for stronger central control.

Training Mandates

As the decade began, the training aspect was assigned to its own task force, led by network personnel and including NCI and support contract staff. It took the “train-the-trainers” curriculum originally used in 1975 to train the CIS and ACS partners and developed a required 36-hour initial training program complete with oral examinations, role-playing, and practice calls. NCI also set in place the requirement for standard certification of all information specialists and the minimal amount of time each specialist was required to spend each week on the phone. In addition, NCI imposed requirements for continuing education and refresher training. As the decade progressed, the need for extensive, systematic, and continuous training for the staff gained importance and structure.

Evaluation Revisited

When DCCR's Board of Scientific Counselors gave approval in 1982 to extend the program for 3 more years, it became clear that concrete evidence of accomplishments would be essential to ensure that the CIS would have a long future. Spurred by this impetus, a three-part evaluation plan was put in place—a standardized Call Record Form, a national user survey, and a system of national test calls.

Call Record Form. A standardized Call Record Form, based on the original form adopted in 1976, was adopted nationwide on January 1, 1983 (32). Pilot tested in three CIS offices, the Call Record Form continues to be used today for every inquiry to the CIS. A broad range of information is coded by each office using some 56 categories, following detailed instructions in an operations man-

ual. A Call Record Form Task Force arbitrates coding disputes.

Data, which are entered in a standard format, are submitted to NCI. At NCI, the data are processed into a single national dataset, as well as into individual office datasets for analysis and management use. Due to Office of Management and Budget (OMB) rules concerning privacy issues, demographic information can be gathered on only 20% of the callers (on randomly selected days assigned to each office by NCI to ensure reliability). Some offices, using supplemental, nongovernment funding, gather data on all callers.

This rich database, which has been made available to researchers, has resulted in studies that have furthered the field of communications in all aspects of the cancer spectrum (see article in this monograph [33]).

Standardization of the user survey. The second arm of the evaluation process, the user survey, was also patterned on work that had its origins in the 1975 Evaluation Task Force.

The restructured Evaluation Task Force played a key role in the design of the new user survey. Several versions of a new survey were pilot tested in four local offices. The new survey was designed to collect data on the following issues: the extent to which the CIS was able to meet the callers' informational needs, the effectiveness of the CIS in affecting the callers' health behavior as compared with other sources, and the extent to which the CIS influenced the health behavior of callers (34). Callers were asked the reason they called, their impressions of the CIS staff, the helpfulness of the information received, and the usefulness of printed materials sent. Key questions were asked to determine whether the CIS was instrumental in modifying callers' health behavior, whether the callers had shared information or referred others to the CIS, and whether they would call again.

The mail survey was distributed to a random sample of CIS users who were sent publications or other material following their CIS call and who called on days randomly selected for each individual CIS office (a ruling from OMB mandated that the survey be sent only to callers who had already given their names and addresses to the CIS). The sample was structured to allow national and local data analysis. A survey coordinator in each office ensured that the user survey methodology was carried out locally, as mandated, with the data analyzed centrally at NCI (34).

From January 1984 through April 1985, over 11 600 surveys were mailed; 7530 were returned (64.7% response rate). An analysis of the national data shows a very high user satisfaction rate: more than 96% of respondents found the information given clear and easy to understand, 94.9% found it helpful, and 97.6% said they would call the CIS in the future for answers to other questions about cancer. Almost 50% of respondents had already recommended the CIS to others at the time they were surveyed. Respondents found the CIS staff knowledgeable (94.8%), courteous (96.8%), and friendly and sympathetic (96.7%). Almost 94% of the respondents were either very satisfied or somewhat satisfied with their overall use of the CIS. In

most cases, those who were dissatisfied (2.1%) were given correct information by the information specialists but did not get the answers they wanted to hear.

Almost 30% of the respondents took time to write comments on their interaction with the CIS (90.3% positive, 5.3% neutral, 4.3% negative). When looking at the service's potential for reaching people other than callers, the survey found the information provided to 4091 callers reached 11 086 people, an almost threefold effect. In addition, more than 93% of the callers surveyed had taken some action following their calls. The three most common actions were reading materials mailed to them (82.7%), sharing the information with at least one other person (58.4%), and making an appointment with a doctor, clinic, or hospital (24.3%). Almost 92% of callers said their contact with the CIS was either very important or somewhat important in making their decision to take a health-related action (32).

A second study used the national user survey data to look at the impact of the CIS on the health-related behaviors of symptomatic callers (35). CIS callers who had cancer-related symptoms at the time of their call, but who had not yet sought a physician's advice, were examined. The study showed that 75% of callers who had not made contact with a health professional before calling the CIS did so after calling the CIS and that of these callers, only 50% indicated that they would have definitely made contact with a health professional on their own initiative—that is, without calling the CIS.

Inauguration of test calls. Since the CIS began, there have been informal "tests" of the system by those interested in determining the accuracy and appropriateness of the information provided—both from within and without the CIS. Beginning in 1980, however, the third arm of the evaluation process was inaugurated: a standardized method for conducting national and local test calls. Designed and pilot tested with the aid of the Evaluation Task Force, the test calls measured three quality dimensions: accuracy (how correct, up-to-date, and complete the information given was), convenience (the accessibility of staff and promptness of response), and appropriateness (whether all questions were answered, requested referrals were given, and appropriate language was used). Staff sensitivity was also judged (how empathetic, friendly, and credible the information specialist was) (36).

The test-call system evolved over time, through trial and error, and with the partnership and trust of the offices. The problems were myriad: how to put into place a system that would be fair to the personnel in the network, yet would accurately judge a program dealing with a complex disease, an enormous range of possible questions, and an ever-changing knowledge base.

Test-call scenarios with questions and minimal expected responses were developed. Background information (such as age and education of caller, disease site, tests performed) were also prepared to be used by the test caller to answer questions posed by the CIS information specialist. Standard scales for each of the quality dimensions were formulated, providing a numerical score for rating each

call. In addition, a procedure for informing offices of the test-call results and for corrective action was instituted. Because the test calls required a major time commitment, NCI estimated it would make two test calls to each office every 6 months. Two persons were needed to make the calls—one to pose as a caller and one to listen and take extensive notes. The same scenarios were used to make a complete round of calls to all offices to judge quality across the network fairly.

The 1983 contracts also mandated test calls at the local level. Most offices used similar scenarios, scoring forms, and rating scales to augment the national system and to ensure monitoring of their own personnel.

The Advent of 1-800-4-CANCER

The single event that most changed the CIS and greatly increased its call volume was new telephone technology that, in 1983, allowed the system to go from 34 different toll-free numbers to the uniform, easily remembered 1-800-4-CANCER.

Originally each regional office had a separate toll-free 800 number. Those offices covering more than one state had different numbers for each state. This plethora of numbers produced significant drawbacks in terms of national publicity and promotion. With new telephone technology, it became possible to convert all the offices to a single 800 number and to route calls automatically to the appropriate local office, according to the area code from which the call was placed. This new capacity signaled a shift from a locally oriented publicity and promotion program to a national one.

Social marketing and promotion. In 1982, the Publicity and Promotion Task Force had adopted several social marketing principles in its promotion plans. These included audience segmentation with separate but complementary promotion strategies for each target audience; selection of target audiences in a readiness stage most likely to respond by calling the CIS; selection of channels appropriate to the target group; use of positive, anxiety-reducing appeals delivered by sources appropriate to the target audiences; clarity through use of a single message (i.e., that immediate benefit could be gained by calling the CIS); and locally developed promotion campaigns that, as much as possible, complemented the message and tone of the network-wide program. The task force had also selected four target groups: persons over 50 years of age, African Americans, smokers who want to quit, and cancer patients and their families (37). The plethora of local CIS 800 numbers made national promotion most unwieldy, however. When television spots were produced, different versions were needed for each area of the country or separate slides were given along with announcer copy to play at the end of the spot. The national print media was unwilling to print 34 toll-free numbers at the end of any major story on the service.

The new 1-800-4-CANCER number presented new opportunities and promotion possibilities and greatly increased the number of calls. In 1982, the CIS received over 233 000 calls. By 1984, that number had grown to over

359 000 calls, an increase of 54%. (An article in this monograph describes the mass-media programs and their effects on the CIS [38].)

ACS begins its own service. In the early 1980s, ACS volunteers and staff concluded that their organization needed a better way to handle calls from the public about cancer issues and began planning what is now called the Cancer Response System (CRS). The CRS, which was opened in a pilot phase in a few divisions in 1984, gradually was adopted by many other divisions across the country. Some divisional areas were handled by a national office. Although at first the CRS was considered competitive by CIS staff, it ultimately was considered a complementary service. By 1990, about 20 000 CRS callers were referred to the CIS for referral and clinical trials information and another 20 000 CIS callers were referred to the CRS for information about ACS local services (39).

Strengthening the Outreach Component

Although the concept of community outreach was addressed in the original contracts, the 1980s saw this component take on new forms. First, "special projects" were inaugurated. Defined as "cancer information/education programs not directly related to the CIS, that are developed to meet the specific information/education needs within the designated service areas" (40), these projects were as diverse as the offices and the populations they served. The CIS office in Minnesota, for instance, capitalized on the strength of the regional print media to reach their largely rural population through a newspaper column. CIS offices in Florida and Massachusetts addressed their large populations of smokers with the establishment of "Smoker's Quitlines" offering specialized counseling to smokers trying to quit. The CIS serving Southern California supported a Black Leadership Initiative designed to encourage African American community leaders to serve as intermediaries to the African American population. The Connecticut CIS targeted allied health professionals, with a nurse-to-nurse consultation program, and education programs for social workers, postmastectomy prosthesis fitters, and the clergy. Special projects were approved by NCI based on their scientific merit and the demonstrated need for the program in the local area.

Many of these projects were successful in their own right. Because they often bore little direct relation to NCI's national priorities, however, the value of the outcomes of the special projects was limited in NCI's eyes. In addition, because the programs were diverse, there was no common objective that could assist the CIS program staff in articulating a generalized statement of the purpose of the special projects. Finally, because of the types of activities involved, many did not include rigorous evaluation components.

These limitations made the special projects vulnerable to program budget cuts. In 1984, in the face of drastic budget limitations, the DCCR administration cut special projects out of the CIS program. Although this decision was justifiable from a division working to establish cancer-control research projects, the elimination of the

outreach staff in the CIS offices significantly jeopardized the ability of OCC to disseminate its cancer information and education messages—OCC lost its local outreach arm to carry out NCI programs in local communities.

Partners in Prevention (PIP). Throughout the history of the program, the local CIS outreach staffs had given assistance to OCC in the local implementation of its education programs and messages. Examples included the “Breast-Self-Examination-in-Hospitals” program and a variety of smoking cessation activities. Just as the DCPC administration cut the CIS special projects, OCC was launching a major Cancer Prevention Awareness Program—Partners in Prevention—a nationwide effort to increase public awareness about the possibilities for cancer prevention and steps that individuals could take to lower their risks of developing cancer. Intensified efforts were directed at two specific risk factors—tobacco and nutrition—and targeted especially at African Americans because of their greater-than-average risk of developing cancer.

In addition to working with a variety of national media activities and major intermediaries, OCC had spent more than 2 years working with the CIS to capitalize on the CIS staffs’ knowledge of their communities and the intermediary organizations that would be ready to undertake NCI education programs. To introduce the program, OCC designed and helped implement seven regional workshops during the spring of 1984. These workshops brought the local CIS offices and their intermediaries together to begin plans for cancer-prevention education activities. PIP was the first major national community education program in which all CIS offices were involved. OCC had carefully orchestrated the effort, with the workshops serving as catalysts, to encourage the development and expansion of cancer-prevention coalitions among the community and the CIS offices.

The program began with significant enthusiasm. Case studies, completed a year later, revealed the importance of having a local contact to keep the program going, a role the CIS was to have fulfilled. “The most important factors associated with relatively active PIP efforts,” said NCI,

were the availability and willingness of the CIS staff members to play a continuing, active role—as leaders and coordinators when the situation required, as supportive advisors or as information resources for participants. Immediately following the PIP workshops, the initiative taken by the CIS coordinators in setting up and leading follow-up meetings was essential. A related factor was the ability of the CIS to commit some staff time to specific activities or areas of activity during subsequent months. Closely connected was the importance of technical support and encouragement provided by the personal participation of NCI staff members and the availability of print materials (41).

The loss of funding for CIS outreach staff limited its ability to follow through on the PIP project. The program

continued but floundered with the loss of the regional CIS staff to serve as its local catalyst for activities.

Funding of outreach by OCC. Following the experience of the PIP program, OCC established Master Agreement Orders (MAOs) for community activities. Restricted to competition by the CIS offices, these MAOs were to provide some funding to carry out programs in the community, as defined by OCC. Although a stop-gap measure, the MAOs provided some aid to both OCC and the CIS in starting some outreach activities. During the next recompetition, OCC offered to support one position in each CIS office for community outreach. Although the offer was made while the CIS program was still housed within DCPC, the positions were not actually included until the 1989 RFP and were not funded until 1990, after the CIS program had moved to OCC (an article in this monograph discusses the outreach efforts of the CIS [42]).

Adding New Technologies

Three technological innovations, in addition to the 1-800-4-CANCER number, were introduced to the CIS network during the 1980s—the Physician Data Query (PDQ) treatment database in 1983, the Publications Ordering Service (POS) in 1985, and electronic mail in 1986. Each, in its own way, brought new strengths and coordination to the network.

PDQ. Although PDQ was not specifically developed for CIS, the database quickly became an invaluable and efficient resource for the network. Each office was provided hardware and software to access the PDQ database, as well as training in its use.

At first, the CIS was restricted to providing information from PDQ only to physicians, due to a decision by the NCAB that there be no promotion of the system to the public. That restriction was soon removed, and the CIS has become PDQ’s most frequent user.

PDQ has become an essential tool for the CIS. Cancer patients and their families and friends accounted for 55% of CIS calls in 1991, and they most frequently request information on treatment. PDQ allows the information specialists to provide callers with timely, state-of-the-art information on treatment options including clinical trials. PDQ information is used as the primary resource on all calls concerning treatment. In addition, nearly 65 000 customized searches have been done to provide information on ongoing clinical trials to patients and families (an article in this monograph discusses the CIS initiative in clinical trials referrals [43]).

Publications Ordering Service. By the mid-1980s, the number of cancer-related NCI publications for patients and the public had greatly increased to a library of over 100 different titles. CIS offices were the local link to ordering these materials, and the new 800 number exacerbated the situation. Although the unified number increased calls, it also increased the rate of busy signals. NCI found it was losing between 11% and 29% of calls to local offices due to busy circuits (44). An analysis of network calls for the last 6 months of 1984 found that approximately 45% of callers were requesting specific

publications (44). This high percentage was partly due to a promotion decision by the Publicity and Promotion Task Force—that offering free booklets was a better way to encourage target audiences to call the CIS than were general health messages—resulting in national promotion campaigns featuring specific NCI booklets.

Early in 1985, AT&T offered a new telecommunications feature, Advanced 800, in which a call-prompter feature would allow callers to choose, by pushing “1” or “2” on their push-button phones, either to order publications or to speak with an information specialist regarding cancer-related questions. Implemented in September 1985, the new service resulted in a drop in call volume in the local offices of approximately 25% (45). Curiously, the POS did not solve the problem of the high busy-signal rate, which remained at 20%. Rather, it changed the complexion of the service in the local offices. Calls from cancer patients and families increased from 24% to 43% of users; calls longer than 6 minutes increased from 23% to 44% of inquiries. Although this technological feature was a solution to callers who only wanted to order publications, it was not without some disadvantages. The instructions confused some callers, especially the elderly, those with less education, and those who did not understand English well. In addition, in the parts of the country where the phone system could not handle the new technology, callers had to listen to the messages in both English and Spanish before they were connected to the CIS.

Electronic mail. One of the major communications problems for NCI and the network—the need to have simultaneous communications with all the offices to alert them to fast-breaking news events or essential management issues—remained a problem without a good solution until 1986, when NCI-furnished computers for accessing PDQ were used to implement another new technology, electronic mail. Messages could be sent to one office, a group of offices, or all offices at once. NCI could, in a second, alert local offices about news and events that could influence the CIS offices and their calls. On the other hand, the local offices could channel necessary local news across the network to ensure that all offices were prepared to respond to calls stimulated by local media on matters that could have a national impact. Any local office could easily send a message to any of the related NCI staff or could communicate with little effort to any other CIS office in the network.

The use of these new technologies ushered the CIS into a new era—one that would continue into the 1990s, with sophisticated equipment helping the information specialists with their challenging task of giving up-to-date, accurate medical information to callers.

Effects of Recompitions

The contract recompitions in the 1980s (1982, 1985, and 1989) were instrumental in bringing about other major changes in the network. Although the basic concept of the national program, derived primarily from the sum of the activities of a series of regional offices, remained intact, the work required by the contracts for each office

became more structured and more uniform with each recompitation.

Opening competition to noncomprehensive centers. A thorny issue in the competition proved to be the opening of the program to noncomprehensive cancer centers in 1982. The cancer centers were no longer considered the “sole source” of potential bidders. As a result, technically acceptable offers were funded from some NCI-designated clinical cancer centers as well as from some community hospitals.

In the mid-1980s, hospitals began to examine the CIS for its marketing value for their cancer programs. Some small local facilities offered to operate the program without cost to NCI. They were allowed to join the network without having to compete in the contract process and without having to perform the full scope of work set out by NCI; under usual circumstances, the work had to be performed according to the contractual agreements. Some other institutions, deemed technically acceptable through the RFP process but not funded, decided to join the network using their own funding sources. It was their hope that being a successful, experienced part of the network would aid them in becoming a funded office in the next round of competition.

By 1987, nine institutions without a contract or funding from NCI had joined the system, with the local institution providing funding for staffing and other support for the CIS offices and NCI providing telephone lines and technical support. The expansion of the CIS program based on these locally funded additions had an effect on the CIS program as a whole. Some of the locally funded offices, unconstrained by the NCI budget limitations and by the need to follow its scope of work, developed rudimentary systems for computerization of the CIS that had not been undertaken before.

On the other hand, the locally funded offices presented significant management challenges to the NCI staff. In an attempt to get a return on their investment in the CIS, some local hospitals began to use the CIS as a marketing tool. This prompted NCI to develop guidelines on the proper use of the CIS name and telephone number and to strengthen its standard operating policies and procedures. Most significantly, the lack of a contract mechanism to maintain accountability for the program jeopardized the stability of the locally funded CIS offices. Although many nonfunded institutions were conscientious in their oversight of the program, others were not. NCI faced overnight closures of offices when sponsoring hospitals decided that the program was no longer “profitable.”

This problem led NCI in 1988 to decide to allow only those institutions deemed technically acceptable through the next RFP process to participate in the network. NCI would sign “zero dollar” contracts with those that were technically acceptable but not within the budget payroll cutoff. These contracts would obligate the institutions to follow the same strict NCI policies and procedures imposed on the funded offices.

The cost-sharing debate. In 1987 the CIS was in an untenable financial situation: it was facing decreasing

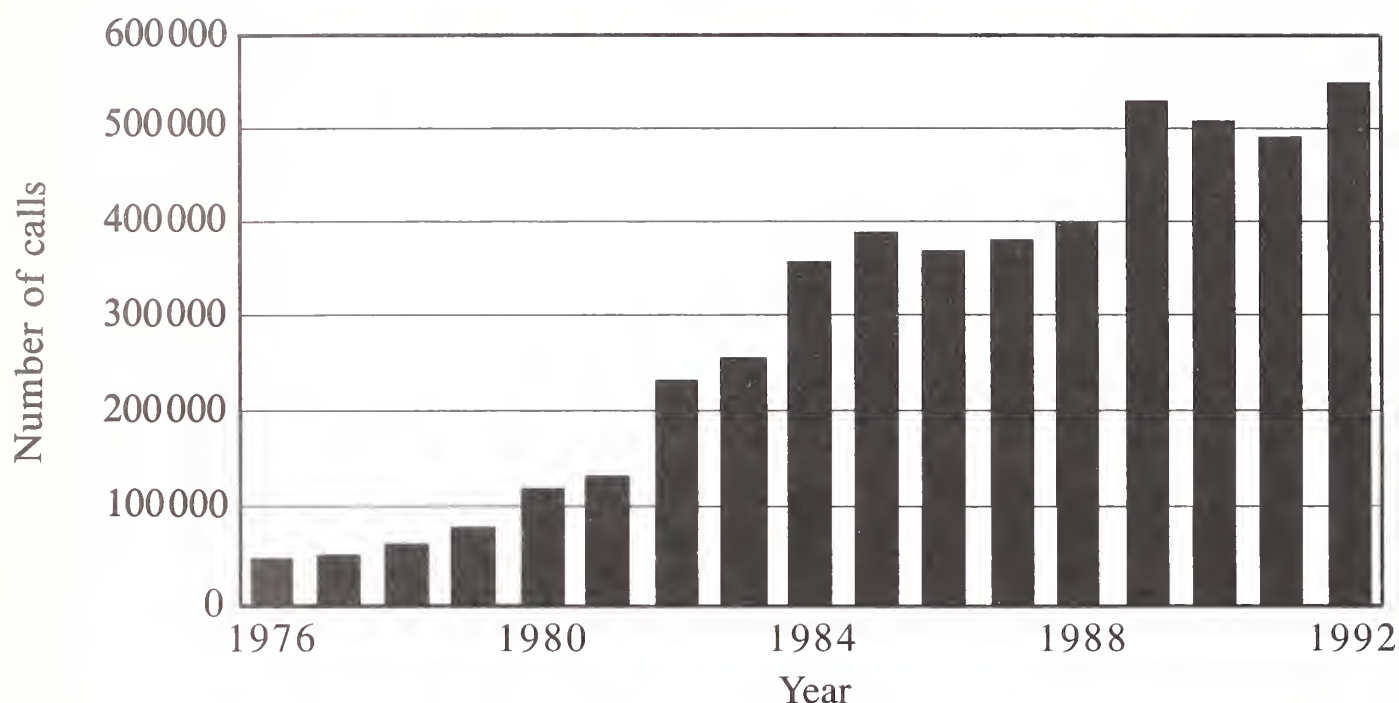


Fig. 1. Cancer Information Service total call volume by year.

support from the Division of Cancer Prevention and Control (DCPC)—formerly called DCCR—while it was experiencing a dramatic, persistent increase in demand for its services from the public (Fig. 1). In an attempt to save the program from almost certain demise, the national NCI program staff in DCPC sought to maintain the program through cost sharing.

In the fall of 1987, at a semiannual CIS meeting, NCI solicited input from the institutions currently holding CIS contracts concerning the feasibility of supporting the network on a cost-sharing basis, with the institutions matching dollar-for-dollar NCI support. The proposal met with a mixed reaction.

The large university-based cancer centers objected to the cost-sharing proposals. They felt NCI was not taking into account the considerable additional costs that were not covered by the contracts—costs that the institutions had been bearing all along. Moreover, NCI had negotiated flat budgets during the preceding 5-year (1982–1987) contract period, at additional substantial expense to many of the centers. The centers believed that the cost-sharing proposal would not save NCI money but instead would add unnecessary paperwork and headaches for the local CIS offices, as well as NCI, in documenting the substantial cost sharing already being carried out.

On the other hand, some freestanding cancer centers and, of course, the locally funded community hospitals (who were presently receiving no NCI funding and would, under the proposal, begin receiving NCI dollars) supported the idea of cost sharing.

In January 1988, the DCPC Board of Scientific Counselors approved the cost-sharing proposal, which was presented by the program staff at the end of the meeting with few board members present. This approval so alarmed some cancer centers that they forced the board to review the proposal in May 1988. As the time for the board's reconsideration drew near, cancer centers and other potential offerors began to take sides. At the meeting itself, the members of the cancer centers opposing the proposal dominated the proceedings and the divided vote defeated cost sharing.

The move to the Office of Cancer Communications. The administration of the CIS program, and where it was best housed within NCI, was a dilemma from the outset. The CIS began in the Communications Branch of DCCR but had OCC, which is located within the Office of the Director of NCI, as a cosponsor. After the Houston meeting in 1975, the program was moved to the Community Activities Branch of DCCR, where the outreach grants and community-based contracts were located. In the early

1980s, as DCCR began to shift its focus from outreach to research, the CIS was moved into the new Education, Research, and Evaluation Branch. In 1983, it was relocated to the Health Promotion Sciences Branch.

By 1985, when DCCR was renamed DCPC, its mission was changing from community service to prevention and control research, applied research, and avoidable mortality. As a service program with a large and still growing budget, the CIS did not fit well into the new research-oriented division. (One attempt was made to make some research activities a part of the CIS. When DCPC Board of Scientific Counselors reviewed the CIS in 1985, it decided to set aside \$1 million to fund communications research projects. The RFP, issued in the fall of 1986, noted that the Cancer Communications System Research [CCSR] monies would be awarded for "studies to initiate cancer communications research activities; the projects could utilize the resources of the CIS." Five studies were funded; each is covered in detail in this monograph [46-50]).

The motivation for the move to OCC, which had continued to be an active CIS cosponsor, was based on the strong ties of the CIS to the information and educational campaigns supported by that office. There was also a sense that the CIS, a service program, was misplaced within the division now dedicated to cancer prevention and control research. Few of the DCPC administrators felt the CIS could survive if it were to be judged by the rigorous scientific standards now required of the division's research programs. The DCPC administration voiced concern that the CIS would not live through another review by the Board of Scientific Counselors and urged the CIS staff to support the move to OCC where there would be more appropriate standards and oversight for the program.

Another reason for the move to OCC was the view, prevailing in NCI's Office of the Director, that the CIS served all of the Institute's programs and that it should be supported by all of the divisions. It was clear that the DCPC should not finance the CIS alone.

NCI's division directors, concerned that they would have to take money "off the top" to finance the CIS in the future, asked OCC to consider centralizing the CIS, thereby eliminating the costs of individual offices. This suggestion reflected a lack of understanding at top levels of NCI that the CIS was more than a telephone service. Because of the visibility of the telephone component, everyone kept forgetting that the CIS was also capable of mounting outreach programs tailored to local needs and supporting NCI-driven education initiatives. In a centralized operation, regional capacity for outreach would have disappeared and the telephone system would have lost the ability to handle questions about local resources. The concept of a decentralized operation ultimately was resold to NCI management based on these latter considerations.

Additional funding found. Finally, in 1989 an RFP promising full funding to successful offerors was released. Twenty-eight proposals were received, and 23 were found to be technically acceptable. The available funding, how-

ever, would cover costs for only eight offices, jeopardizing the viability of a national network and the continued funding of some of the very centers that fought the cost-sharing proposal. Faced with a seemingly impossible situation, OCC proposed a shortening of the contract period from 5 to 2½ years to absorb the total program costs in a shorter time. This move saved six additional offices. When OCC realized that this was the best that they could do, they took this proposed funding scheme and the list of institutions that would not be funded to Samuel Broder, M.D., Director of NCI. In an unprecedented show of support for the CIS program, Dr. Broder provided funding for four additional CIS offices to ensure a more equitable geographic coverage of the country by local CIS offices. The 1989 funding came with the provision that OCC examine the program to explore alternative, more cost-effective program structures and funding mechanisms.

Although the overall number of offices has never changed dramatically from contract to contract, the specific offices in the CIS network have changed. Each time, some offices were deleted and replaced by "new" offices not originally in the network. Others that had been CIS offices dropped out at one competition and later "won" their way back into the network (Table 3). Although approximately 80% of the U.S. population has always been covered by the local CIS offices, it has not always been the same population. The entire country, however, has always had access to the CIS network through the national office. Eight cancer centers have held contracts consistently since 1975—Dana-Farber, Fox Chase, Johns Hopkins, M. D. Anderson, Memorial Sloan-Kettering, Roswell Park, University of Miami, and Yale University.

The CIS closed the decade of the 1980s as a much more mature service, a service that had grown in stature with mechanisms in place to share its many accomplishments (Table 4). It had successfully overcome many obstacles and achieved major success in running and maintaining a high-quality communications system.

THE YEARS OF EXPANSION AND TECHNOLOGICAL OPPORTUNITY—THE 1990s

As the 1990s began, the words of Winston Churchill, "Give us the tools and we'll finish the job," (51) could have aptly applied to the CIS.

After joining OCC in 1988, the CIS was strengthened, streamlined, and consolidated in many areas. OCC made a major commitment to the program, which it welcomed as a kindred spirit. Program staff increased, semiannual meetings were restored, and the circular memos were translated into standard operating policies and procedures. Community outreach coordinator positions were reestablished in the local CIS offices.

Joining the Reports and Inquiries Branch

In OCC, the CIS became integrated into the Reports and Inquiries Branch. Ties were cemented between the

Table 3. CIS contractors and local CIS offices—1975–1993

1975 (17 funded)			1978 (17 funded)			1982 (17 funded, 4 unfunded)			1985 (16 funded, 9 unfunded)			1990 (18 funded, 4 unfunded)			1993 (19 funded)		
State and location	Area covered*	State and location	Area covered*	State and location	Area covered*	State and location	Area covered*	State and location	Area covered*	State and location	Area covered*	State and location	Area covered*	State and location	Area covered*	State and location	Area covered*
AL/Comp Ca Ctr Univ of Alabama	AL	CA/Univ of Calif at Los Angeles†	So CA	AL/Comp Ca Ctr Univ of Alabama†	AL	CA/Univ of Calif at Los Angeles†	AL	AL/Comp Ca Ctr Univ of Alabama†	AL	CA/Univ of Calif at Los Angeles†	AL	AL/Comp Ca Ctr Univ of Alabama†	AL	AL/Univ of Alabama	AL, LA, MS		
CA/Univ of So Calif Ca Ctr	So CA	CA/Univ of So Calif Ca Ctr	So CA	CA/Univ of So Calif Ca Ctr Univ of Los Angeles	So CA	CA/Univ of So Calif Ca Ctr Univ of Los Angeles	So CA	CA/Univ of So Calif Ca Ctr Univ of Los Angeles	CA	CA/Univ of Calif at Los Angeles	CA	CA/Univ of Calif at Los Angeles	W CA	CA/Univ of Calif at Los Angeles	So CA		
CO/Colorado Regional Ca Ctr	CO	CT/Yale Univ Comp Ca Ctr	CT	CO/Penrose Ca Hospital	CO	CO/Penrose Ca Hospital	CO	CO/Penrose Ca Hospital	CO	CO/Penrose Ca Hospital	CO	CO/Penrose Ca Hospital	CO, NM, WY	CA/No Calif Ca Ctr	No CA, NV		
CT/Yale Univ Comp Ca Ctr	CT	DC/Georgetown-Howard Ca Ctr	DC	CT/Yale Univ Comp Ca Ctr	CT	CT/Yale Univ Comp Ca Ctr	CT	CT/Yale Univ Comp Ca Ctr	CT	CT/Yale Univ Comp Ca Ctr	CT	CT/Yale Univ Comp Ca Ctr	CT, RI	CO/Penrose Ca Hospital	AZ, CO, So ID, NM, UT, WY		
DC/Georgetown-Howard Ca Ctr	DC	FL/Sylvester Comp Ca Ctr (Miami)	FL	FL/Sylvester Comp Ca Ctr	FL	FL/Sylvester Comp Ca Ctr	FL	FL/Sylvester Comp Ca Ctr (Miami)	FL, GA	FL/Sylvester Comp Ca Ctr (Miami)	FL, GA	FL/Sylvester Comp Ca Ctr (Miami)	FL, GA, PR	CT/Yale Univ Comp Ca Ctr	CT, ME, MA, NH, RI, VT		
FL/Sylvester Comp Ca Ctr (Miami)	FL	IL/Illinois Ca Council	IL	DC/Howard Univ Ca Ctr	DC	FL/Sylvester Comp Ca Ctr (Miami)	FL, GA	HI/Univ of Hawaii	HI	HI/Univ of Hawaii	HI	HI/Univ of Hawaii	HI	FL/Univ of Miami	FL, PR		
IL/Illinois Ca Council	IL	MA/Dana-Farber Ca Inst	MA, ME, VT, NH	FL/Sylvester Comp Ca Ctr (Miami)	FL, GA	HI/Univ of Hawaii	HI	IL/Illinois Ca Council	IL	IL/Illinois Ca Council	IL	IL/Illinois Ca Council	IL	HI/Univ of Hawaii	HI		
MA/Dana-Farber Ca Inst	MA	MD/Johns Hopkins Univ Comp Ca Ctr	MD, parts of PA, WV	HI/Univ of Hawaii	HI	IL/Illinois Ca Council	IL	KY/Markey Ca Ctr§	KY	KY/Markey Ca Ctr§	KY	KY/Markey Ca Ctr	KY	KS/Univ of Kansas Med Ctr	IL, KS, MO, NE		
MD/Johns Hopkins Comp Ca Ctr	MD, parts of PA, WV	MN/Mayo Clinic	MN	KY/Ephraim McDowell Ca Network§	KY	MA/Dana-Farber Ca Inst	MA, ME, NH, VT	MA/Dana-Farber Ca Inst	MA, ME, NH, VT	MA/Dana-Farber Ca Inst	MA, ME, NH, VT	MA/Dana-Farber Ca Inst	MA, ME, NH, VT	KY/Markey Ca Ctr	AR, KY, TN		
MN/Mayo Clinic	MN	NC/Duke Univ Comp Ca Ctr	NC	MA/Dana-Farber Ca Inst	MA, ME, NH, VT	MD/Johns Hopkins Comp Ca Ctr	MD	MD/Johns Hopkins Comp Ca Ctr	MD	MD/Johns Hopkins Comp Ca Ctr	MD	MD/Johns Hopkins Comp Ca Ctr	MD	MD/Johns Hopkins Comp Ca Ctr	MD, No VA, DC		
NC/Duke Univ Comp Ca Ctr	NC	NY/Memorial Sloan-Kettering Ca Ctr	NYC	NY/Memorial Sloan-Kettering Ca Ctr	NYC	MI/Comp Ca Ctr of Metropolitan Detroit	MI	MI/Comp Ca Ctr of Metropolitan Detroit	MI	MI/Comp Ca Ctr of Metropolitan Detroit	MI	MI/Comp Ca Ctr of Metropolitan Detroit	MI	MI/Comp Ca Ctr of Metropolitan Detroit	IN, MI		
NY/Memorial Sloan-Kettering Ca Ctr	NYC	NY/Roswell Park Memorial Inst	NY	MD/Johns Hopkins Comp Ca Ctr	MD	MI/Comp Ca Ctr of Metropolitan Detroit	MI	MN/ACS and Mayo Clinic†	MN	MN/ACS and Mayo Clinic†	MN	MI/Comp Ca Ctr of Metropolitan Detroit	MI	NC/Duke Univ Comp Ca Ctr	GA, NC, SC		
NY/Roswell Park Memorial Institute	NY	OH/Ohio State Univ Comp Ca Ctr	OH	MI/Comp Ca Ctr of Metropolitan Detroit	MI	MI/Comp Ca Ctr of Metropolitan Detroit	MI	MO/Boone Hospital Ctr§	MO	MO/Boone Hospital Ctr§	MO	NC/Duke Univ Comp Ca Ctr	NC, SC	NY/Memorial Sloan-Kettering Ca Ctr	NYC, LI, Westchester Co		
PA/Fox Chase & Univ of Penn Comp Ca Ctr	PA, DE, NJ	PA/Fox Chase & Univ of Penn Ca Ctr	PA, DE, NJ	MN/Mayo Clinic	MN, SD, ND	MN/Mayo Clinic	MN, SD, ND	NC/Duke Univ Comp Ca Ctr†	NC	NC/Duke Univ Comp Ca Ctr†	NC	NY/Memorial Sloan-Kettering Ca Ctr	NYC, LI, No NJ	NY/Roswell Park Memorial Inst	NY, W PA		
TX/Univ of Texas M D Anderson Ca Ctr	TX	TX/Univ of Texas M D Anderson Ca Ctr	TX	NC/Duke Univ Comp Ca Ctr	NC	NC/Duke Univ Comp Ca Ctr	NC	NY/Memorial Sloan-Kettering Ca Ctr	NYC, LI, No NJ	NY/Memorial Sloan-Kettering Ca Ctr	NYC, LI, No NJ	NY/Roswell Park Memorial Institute	NY	PA/Fox Chase Ca Ctr	E PA, DE, NJ		

Table 3. CIS contractors and local CIS offices—1975-1993—Continued

1975 (17 funded)		1978 (17 funded)		1982 (17 funded, 4 unfunded)		1985 (16 funded, 9 unfunded)		1990 (18 funded, 4 unfunded)		1993 (19 funded)	
State and location	Area covered*	State and location	Area covered*	State and location	Area covered*	State and location	Area covered*	State and location	Area covered*	State and location	Area covered*
W/Fred Hutchinson Ca Research Ctr	WA	W/Fred Hutchinson Ca Research Ctr	WA	NY/Memorial Sloan-Kettering Ca Ctr	NYC, LI, No NJ	NY/Roswell Park Memorial Inst	NY	OH/Ohio State Univ Comp Ca Ctr	OH	TX/Univ of Texas M D Anderson Ca Ctr	TX, OK
WI/Univ of Wisconsin Comp Ca Ctr	WI	WI/Univ of Wisconsin Comp Ca Ctr	WI	NY/Roswell Park Memorial Institute	NY	OH/Ohio State Univ Comp Ca Ctr†	OH	PA/Fox Chase Ca Ctr	PA, DE, So NJ	W/Fred Hutchinson Ca Research Ctr	AK, No ID, MT, OR, WA
		Biospherics	Rest of country	OH/Ohio State Univ Comp Ca Ctr†	OH	OK/Oklahoma Ca Info Svc§	OK	TN/Thompson Ca Survival Ctr†	TN	WI/Univ of Wisconsin Comp Ca Ctr	WI, MN, IA, ND, SD
				PA/Fox Chase Ca Ctr	PA, DE, So NJ	PA/Thompson Ca Survival Ctr§	PA, DE, So NJ	TX/Univ of Texas M D Anderson Ca Ctr	TX, LA	WV/Mary Babb Randolph Ca Ctr	OH, So VA, WV
				TX/Univ of Texas M D Anderson Ca Ctr	TX	TX/Univ of Texas M D Anderson Ca Ctr	TX	UT/Univ of Utah	UT		
				W/Fred Hutchinson Ca Research Ctr†	WA	UT/St Benedict's Hospital§	UT	WV/Mary Babb Randolph Ca Ctr	WV, VA		
				WI/Univ of Wisconsin Comp Ca Ctr	WI	W/Fred Hutchinson Ca Research Ctr	WA	Biospherics	Rest of country		
				Biospherics	Rest of country	WI/Univ of Wisconsin Comp Ca Ctr	WI				
						WV/Mary Babb Randolph Ca Ctr	WV				
						Biospherics	Rest of country				

*Coverage of some states phased in during contract period.

†Psychosocial counseling line.

‡Technically acceptable but not funded; operating under local funding.

§Added to network without going through RFP process.

Table 4. Chronology of CIS events—the 1980s

November 1980	Standardized training program inaugurated
November 1980	Standardized methods of doing test calls, both locally and nationally, inaugurated
January 1982	Third set of 17 contracts awarded in open competition
February 1982	National Plan for Publicity and Promotion of the CIS revised to include selected target groups (persons over 50, African Americans, smokers who want to quit, and cancer patients and their families)
January 1983	National Evaluation Plan put into place, with common Call Record Form and national data analysis
February 1983	Special Projects component for outreach inaugurated
March 1983	1-800-4-CANCER—national CIS number—inaugurated
May 1983	Antismoking media campaign, featuring Surgeon General C. Everett Koop, launched
October 1983	PDQ—computerized Physician Data Query—system dedicated
January 1984	National user survey began
February 1984	Fifth National Cancer Communications Conference, Washington, D.C.
March 1984	American Cancer Society Cancer Response System inaugurated
March 1984–May 1985	Prevention Awareness Campaign conducted
May 1984	Partners in Prevention regional workshops held
May 1985	NCI Cancer Prevention Awareness Program for Black Americans launched in Detroit; Aretha Franklin PSAs run
May 1985	Fourth set of 17 CIS contracts awarded
June 1985	President Reagan diagnosed with colon cancer
November 1985	National Publications Ordering Service—to fill requests for publications—implemented
December 1985	Interleukin-2 (IL-2) preliminary report published
September 1986	Cancer Communications System Research RFP issued
October 1986	Electronic mail system implemented
December 1987	Master Agreement Order for OCC Community Support awarded
September 1988	National responsibility for CIS moved to Reports and Inquiries Branch of OCC
October 1988	Clinical trials training conducted
September 1989	Prostate Cancer Awareness Campaign conducted

national CIS office and local offices, creating new program uniformity and continuity. Resources and technical expertise, such as answers to difficult cancer questions or NCI policy questions, were provided to the CIS by the Public Inquiries Office. The CIS relies heavily on Public Inquiries and the Press Office—all now members of the same branch—for quick, accurate responses to the public's questions spurred by breaking news stories on cancer.

Having all three components in one branch allowed faster communications, uniform responses, and greater accountability. By joining OCC, the CIS also took on an integral role in the planning process for educational projects—NCI initiatives targeted at special populations. The support of OCC has brought a new infusion of energy and fresh opportunities for the CIS to serve as key “field offices” for NCI initiatives and to provide the latest cancer information, translating research progress into practice in American communities.

Management of the network. The management style that was put in place after the Houston meeting in 1975—a partnership between NCI and the contractors, with strong task forces made up of staff members from the local and national CIS offices and with semiannual meetings for discussion and problem solving—has persisted throughout the history of the CIS.

This management system was strengthened with the move to OCC. Additional project staff was hired (national program staff increased from one half-time position in 1980 to six full-time positions today). The augmented staff strengthened NCI's ability to provide needed national leadership for coordinating the efforts of the field and for bringing about uniformity in the local offices.

The task force system was also re-energized to facilitate the operation, coordination, and management of the network. Some of the original task forces were still in effect: Evaluation; Publicity and Promotion, with its name later changed to Promotion and Outreach; Management, now called Policies and Procedures; and Training, now called Staff Training. New task forces were added: Staff Development, Information Resources, and Special Populations. Each is chaired by field staff, with members chosen by the chair, subject to the approval of the project officer, who provides oversight to the task-force operation. Each task force has a specific mission statement and is responsible for assisting in the development and management of its program area.

The semiannual meetings were reformatted to allow for working sessions on topics generated from both the field and NCI. Sessions are led by the field staff and/or NCI staff, depending on the subject being discussed. New programs are planned by the task forces, then presented for review and discussion at the semiannual meetings by field staff task-force members, rather than being presented as mandates by the national staff.

Throughout the history of the CIS, the management principles have remained the same: the details of how the work of the CIS is fashioned are decided on through a cooperative working relationship, with both the field and

national staffs playing important roles in the decision-making process. This system of governance has served the program well. It has allowed the expertise at both NCI and the field to be utilized (*see* Table 5 for background of CIS staff), fostering not only new ideas and technology transfer but also feelings of cooperation and unity among the disparate offices.

Streamlining the Program

As OCC sought adequate resources for the CIS, it also turned its attention to improving technology, upgrading quality assurance and training, and defining the role of the community outreach coordinator.

New technology. New technology included a new telephone system and a new computer system. In 1991, conversion of the CIS Advanced 800 telephone system to the federal government's telephone service FTS 2000 was completed. FTS 2000 offered the CIS advanced telecommunications technology, such as improved call-routing capabilities, electronic mail, and data-transmission enhancements that improved service and provided significant cost savings. The CIS, the first government program to undertake this conversion, required over a year of planning and coordinating telecommunication services at all CIS offices across the country.

The CIS adopted CD-ROM computer technology to provide consistent, more cost-efficient PDQ searching for cancer patients and their families. Providing the complete database to each office on a compact disc eliminated

online searching costs and improved response times. Each CIS office was furnished equipment to access PDQ in this new manner.

Advances in electronic mail technology in the 1990s have further enhanced NCI's ability to communicate with the local offices quickly. For instance, when media stories reported taxol as a new cancer treatment, NCI prepared a response and sent it via electronic mail, giving prompt, uniform, accurate information to all offices. Policy and administrative issues, difficult or unusual inquiries, meeting agendas, or fact sheets can be transmitted electronically in camera-ready, reproducible form, eliminating the need for frequent mass mailings.

In the meantime, the public demand on the CIS had been increasing dramatically. The service handled nearly 500 000 calls in 1991. The busy signal rate hovered around 50% because funds were not available to add additional telephone lines and staff. Significant relief came in 1992 when NCI funded an additional 25 lines and 48 staff positions to those offices with the highest busy-signal rates.

National test-call system. As the public's demand on the CIS continued to increase, not only in terms of call volume but also in terms of the length and complexity of calls on a wide range of topics, OCC has supported increased quality-assurance measures, including standardized training, site visits, electronic mail, standardized program reporting, and mandated call monitoring. Although the original national test-call system continued throughout the 1980s, it became apparent that it did not have the breadth

Table 5. Qualifications of regional CIS staff

Position (No. of staff members)	Degree	Length of service with CIS	Other
Project director (19)	Most possess a master's degree in public health, social work, education, or arts. Two have doctoral degrees.	Average length of service is 8 years; spans from less than 1 year to 17 years.	Eight of the project directors have come up through the ranks, beginning as information specialists on the telephone.
Telephone service manager (19)	All possess a nursing degree or a bachelor's degree; several have either a master's degree or are studying for it.	Average length of service is 6 years; spans from less than 1 year to 17 years.	Ten of the telephone service managers have come up through the ranks, beginning as information specialists on the telephone.
Information specialist (120)	Vast majority have a bachelor's degree in either science or the arts; several have a nursing degree; three are medical students.	Average length of service is 3 years; spans from less than 1 year to 17 years.	Many have counseling and teaching backgrounds; several are nurses; several are Hospice volunteers; many are bilingual in English and Spanish, French, or Italian.
Community outreach coordinator (19)	Almost all have a bachelor's degree; 10 have a master's degree either in public health, education, social work, or communications; one has a doctoral degree in higher education.	Average length of service is 3 years; spans from less than 1 year to 8 years.	Two are former CIS information specialists; several have backgrounds in marketing, public relations, and teaching.

and depth to give a true reading of quality assurance across the program.

In 1991, CIS program staff at OCC working with the Applied Research Branch of DCPC developed a new national test-call program—the Cancer Information Service Telephone Evaluation and Reporting System (CISTERS)—that involves placing computer-assisted simulated calls. Utilizing pretested and approved scenarios of typical questions, NCI staff will place calls to CIS offices. The calls will be evaluated on the basis of accuracy of response, compliance with national policies, credibility, convenience, and communications skills. Approximately 4000 calls per year will be placed to ensure that the evaluation is based on a representative sample of calls. CISTERS, described in detail in an article in this monograph (52), offers a new management tool at the national level, more feedback to local offices, and assistance in identifying and directing training and resource needs.

Revised training program. In 1990, the Staff Training Task Force reviewed the procedures and materials being used to train CIS information specialists. An assessment of the training programs in all 23 offices was conducted. Based on this assessment, a new model was developed that has become the blueprint for revising the training program.

The key element of this new model is to focus on the structure and needs of a call to the CIS, rather than to use a didactic approach to learning about multiple cancer sites and the various types of cancer treatment. The CIS information specialist is taught how to structure a call in a logical way so that key information specifically tailored to the caller can be given.

To test this new approach, a full training module on breast cancer was developed, pilot tested, and introduced throughout the network. Breast cancer was chosen not only because it is the site most frequently asked about but also because the information to be disseminated is so complex. Breast cancer call guides were developed based on key intervention points in the disease process (diagnosis, biopsy, primary treatment, follow-up care, and recurrence). The elements of a call were identified (type of caller, background assessment, goals of the call, key information to be provided and where to find it among available resources, coping/support issues, and key referrals). A glossary of terms was also developed to help information specialists define complex medical terms in a consistent fashion.

The call guides and the structured approach to dealing with a call to the CIS have a parallel in the CISTERS program. The key elements that CISTERS evaluates are the same elements that form the structure of the training program. In this way, NCI will be able to evaluate the effectiveness of its training program through the quality of the test calls that are placed.

Continuing education programs are also being developed to follow this approach. The most recent addition is a program on responding to calls about cancer pain. Training programs that address other key elements of the CIS program are also under way. These include training

and orientation for managers and outreach coordinators that focus on necessary skills to manage expanded staff and increased responsibilities effectively. These skills include supervising staff, speaking to groups, working with intermediaries, and conducting training sessions.

Restructuring Outreach

The outreach coordinator positions were restored in the 1989 RFP, but local offices were not given funding to hire the new staff until October 1990, 6 months after the new CIS contracts were awarded. In most offices, this job was held by a single person; however, a few offices with large or diverse populations had two staff members. There was considerable discussion about the type of person needed for this position. Although OCC attempted to give some guidance by providing the offices with a generic job description, the experience and background of the staff hired for these positions varied greatly. Some community outreach coordinators, as the new position was called by NCI, had degrees in health education; others had more media-related backgrounds and experience. This diversity made the effort to define the role of the outreach coordinator more difficult. NCI made it clear, however, that the primary direction in the outreach activities would shift to an emphasis on national initiatives. In this way the CIS would be directly contributing to the goals and objectives of the institute.

Shift to a catalytic role. OCC continues to work with the CIS to shape the outreach program. Although the program is still evolving, it is clear that the role of the CIS outreach staff has changed substantially since 1980, when the offices were carrying out special projects. Because the offices are now responsible for implementing nationally developed education initiatives, the role of the CIS outreach coordinator has shifted away from that of a health educator toward that of catalyst or facilitator. The outreach coordinator is no longer responsible for conducting local education activities. Rather, the outreach coordinator must identify appropriate intermediaries to implement nationally developed programs. Thus, the CIS has taken on more of a networking role and focuses on training others to implement programs to achieve a common goal.

Emphasis on underserved audiences. Following NCI program priorities to address the underserved, each CIS office is responsible for identifying at least one of four NCI-designated target audiences as the focus for its education efforts. These include African Americans, Hispanic Americans, older Americans, and populations with low literacy rates. Each CIS office then develops a yearly outreach plan targeting its selected special population(s). Outreach programs focus on audiences underrepresented in the CIS call volume (several articles in this monograph discuss the issues surrounding reaching these target audiences [48,53–55]).

The first national education initiative under the new outreach parameters is to increase breast-cancer screening in women age 40 and over. This is to be accomplished through the media and through activities with local intermediary groups. The CIS offices are utilizing nationally

developed materials, including intermediary kits and a nationally produced, 30-minute broadcast video, to spark local interest and support for the initiative. CIS intermediary activities include efforts to target work sites, churches, and community health clinics with mammography education materials. The outreach component is described in detail in an article in this monograph (42).

Unresolved outreach issues. Although the community outreach component of the CIS is beginning to flourish as the CIS outreach coordinators expand intermediary contacts, several issues still need to be resolved.

There is currently no sound evaluation strategy to document the activities undertaken in community outreach. Although the current structure dictates the target audiences to be reached, the program does not currently attempt to reach those audiences in a structured or formalized manner. Outreach coordinators are challenged to develop local programs using national materials. No specific guidance, however, has been provided to them on model programs that might be used to develop these local activities.

There is concern that development of "model" programs might stifle community interest and involvement in the programs, but this lack of standardization may make it difficult to evaluate the relative effect of the program. The challenge to OCC will be to identify the appropriate balance of structure that will ensure that the programs generated in the community are sufficiently grounded in communications research yet allow for flexibility in local implementation.

Program Review and New Concept Approval

While OCC continued its efforts to streamline the CIS as it entered the 1990s, funding remained an enormous question mark. The CIS faced yet another critical challenge to its continued viability. Maintaining an effective program required escalating resources at a time of tight federal dollars—putting the CIS in direct competition with other major demands for funds within the NCI. Would it be possible to obtain continued funding for the CIS and, if so, what kind of resources and what kind of program would emerge, based on available dollars?

Time was short. The local CIS and the national office contracts were scheduled to end late in 1992 and early in 1993, respectively. To continue the service uninterrupted, the NCI Executive Committee and the NCAB needed to review and approve a new concept and funding plan for each of the programs in time to develop and release new RFPs by late 1991. If this timetable were kept, the new contracts could get under way without a break in service.

The use of the CIS was under increasing public demand. There was also the need for increasing resources, a need that, in turn, raised questions. How effective and efficient was the service? What changes should be made? Were there cost-saving measures or other alternatives to consider in operating it? Was the CIS a priority of NCI in economically tough times?

Outside management review. To step back and help look at these issues, OCC commissioned a review of the

program by outside consultants. The program had never been held to such close scrutiny. The management review was to develop and present cost-effective future options.

The 2-year management review, completed in 1991, explored alternative program structures and new technologies in an effort to improve the level, quality, and cost-effectiveness of the CIS program (56). The review included discussions with current CIS program and field staff, cancer center directors, and senior NCI staff. Persons outside the system, such as ACS staff, were also contacted. In addition, the study examined other 800 and 900 telephone services and explored technological and fiscal opportunities currently available. The final report summarized the structural, technological, and fiscal alternatives for the CIS program.

On the basis of the management review, OCC proposed a new program structure, first to the NCI Executive Committee and then to the NCAB, calling for a complete decentralization of the CIS program. The proposed reorganization was designed to create a more equitable level of service to the American public by serving the entire country with regional offices.

Reorganized CIS. This reorganization capitalized on the effectiveness of a decentralized program structure while taking advantage of available technology to ensure the most efficient operation of the program. Specifically, the OCC proposal included the following:

- 15–20 regional offices, each serving 15–20 million individuals.
- Regions designated by NCI; offerors could bid only for an entire region(s), rather than choosing specific states to cover.
- Nighttime coverage handled at one of the regional offices, eliminating the duplication of resources in a national office.
- Advanced call-routing telecommunications technology allowing calls to be redirected by NCI from one office to another on a planned or emergency basis.
- Increase in the number of WATS lines by 20% nationwide.
- Expansion of outreach capabilities to allow the CIS regional staff to help facilitate the outreach efforts of NCI-designated cancer centers and other NCI-funded intermediaries.

Final concept approval was received from the NCAB in May 1991. Public comment on the proposed geographic regions was received during an open forum in June and through written comments.

The configuration of the new network presented issues to NCI that were difficult to resolve. The change in areas to be covered had the potential of eliminating some offices that had been in the network since its inception. It would also result in putting existing offices into direct competition with each other for the first time. With given resource limitations, great efforts were made by OCC to divide the country into the most equitable and demographically sensitive regions, with care given to established referral patterns (Table 6). The final configuration of the network, with 19 regions, was released with the RFP in January

Table 6. Reconfigured regions—1992

Region No.	Area covered	Population
1	Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont	13.1 million
2	New York City, Long Island, Westchester County	10.0 million
3	New York state (excluding New York City, Long Island, Westchester County), Western Pennsylvania (area codes 412, 814)	14.1 million
4	Delaware, New Jersey, Eastern Pennsylvania (area codes 215, 717)	14.5 million
5	District of Columbia, Maryland, Northern Virginia (counties of Arlington, Fairfax, Loudoun, Prince William, Stafford)	6.3 million
6	Georgia, North Carolina, South Carolina	16.9 million
7	Florida, Puerto Rico	16.1 million
8	Alabama, Louisiana, Mississippi	11.6 million
9	Arkansas, Kentucky, Tennessee	11.2 million
10	Ohio, Southern Virginia (all Virginia counties except those in Region 5), West Virginia	17.8 million
11	Iowa, North Dakota, Minnesota, South Dakota, Wisconsin	13.3 million
12	Indiana, Michigan	14.8 million
13	Illinois, Kansas, Missouri, Nebraska	20.9 million
14	Oklahoma, Texas	21.0 million
15	Alaska, Northern Idaho (counties of Benewah, Bonner, Boundary, Clearwater, Kootenai, Latah, Lewis, Nez Perce, Shoshone), Montana, Oregon, Washington state	9.5 million
16	Arizona, Colorado, Southern Idaho (all Idaho counties except those in Region 15), New Mexico, Utah, Wyoming	11.6 million
17	Northern California (all California counties except those in Region 18), Nevada	15.0 million
18	Southern California (counties of Imperial, Inyo, Kern, Kings, Los Angeles, Orange, Riverside, San Bernadino, San Diego, San Luis Obispo, Santa Barbara, Tulare, Ventura)	15.0 million
19	Hawaii	1.1 million

1992 (Fig. 2), with contracts scheduled to be awarded in April 1993.

Recompetition 1992

The CIS has been sustained as a viable program during lean years of level budgets and program cuts because of a dedicated staff both at NCI and at the local offices. With the resources available under the new contracts, the program has many opportunities to serve as a national resource.

Key program changes in the RFP that will influence the program include the recognition that the CIS offices will serve as field offices for NCI, facilitating and encouraging local adoption and adaptation of OCC information and education programs (57).

Priorities and opportunities. The new contracts present the priorities and opportunities for the rest of the decade. The CIS has been encouraged to build new relationships and community links, while it strengthens old ones. Two of the most long-standing are with ACS and the NCI-

designated comprehensive cancer centers. In 1991, the ACS and CIS program leaders met and agreed on the complementary status of their respective services. Program staff also have begun close working relationships, attending each other's national meetings and serving as consultants in their respective program development. In the meantime, CIS offices are building bridges with ACS counterparts for outreach activities.

Originally, the CIS had been closely connected with NCI's comprehensive cancer centers. Since many of the offices continue to be located at these centers, the connection has remained strong, even after other noncomprehensive cancer centers joined the network. In the early 1990s, closer links with centers were encouraged by OCC and the NCI centers' program staff. When NCI developed new guidelines for criteria for comprehensiveness of centers, it required some level of cooperation between the centers and the local CIS office. This requirement did not mean a CIS contract per se was necessary. Language in the new CIS contracts also requires their cooperation with cancer centers. Centers and the CIS have been pushed to

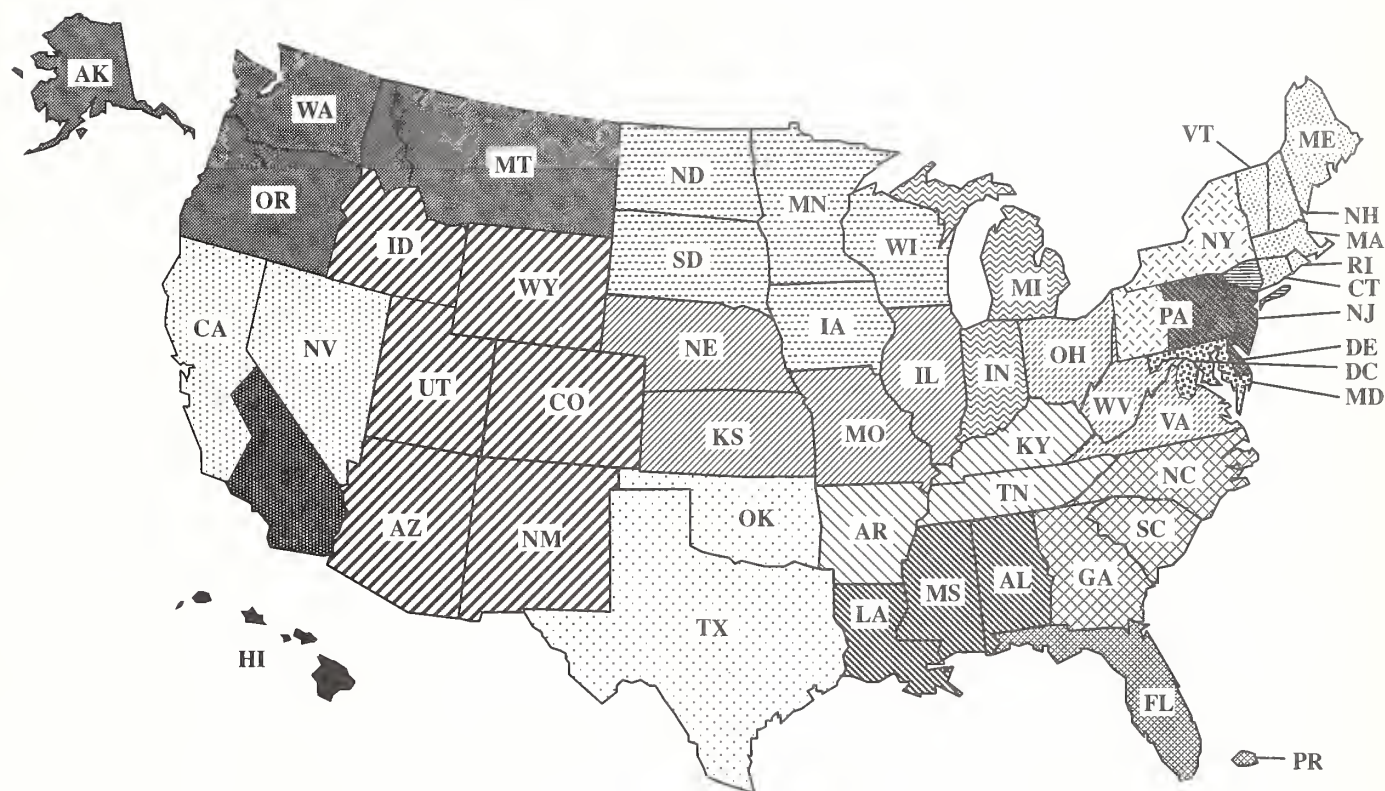


Fig. 2. Nineteen Cancer Information Service regional service areas.

capitalize on each other's resources by seeking areas of mutual interest and cooperation, avoiding duplication of effort (such as other telephone information services at centers), and strengthening community outreach to the credit of both.

Community outreach under the new contracts has been redefined and expanded. For the first time, equitable coverage is possible nationwide. Outreach will, however, encompass large populations and geographic regions, calling for new management and networking skills. It offers cancer centers a special opportunity for working with the CIS to reach their populations. The role of the community outreach coordinator is to unify and strengthen. The coordinator works as a catalyst and coordinator with a wide range of organizations and intermediaries to empower major regional educational programs. Enduring relationships can be nurtured, bringing new programs to life throughout the region.

The telephone service also has room to grow while maintaining the gold standard of accurate, timely cancer information. It can now develop and standardize directories of local resources for all areas of the country, explore the value of proactive calls (such as encouraging appropriate screening for breast cancer), and find better ways to

meet the needs of underserved populations in a culturally sensitive manner.

A focal point of the CIS is to reach the underserved through both the telephone service and outreach programs and to consider ways to link the two more closely. The service can continue to be a leader in taking advantage of cost-efficient technologies and new tools, such as databases, that bring together, at a community level, information on demographics, media habits, and health practices.

The enhancement of the new research and evaluation capabilities of the CIS is also underscored in the new CIS contracts, encouraging the program to be a crucible for communications research (33). Through efficient data-retrieval systems, the CIS will continue to be a valuable resource of cancer-related data for NCI and other programs. Offices can also consider a variety of research projects and remain rigorous in applying evaluation criteria to discern the outcome of program efforts.

Long-Term Commitment

OCC proposed that the newly structured CIS be budgeted for 10 years to give stability and strength to a regional network of this size and scope. There was support

for a long-term commitment to the CIS at the highest levels at NCI but with the understanding that funds each year depended on overall NCI funding from yearly congressional appropriations. The issue of whether or not the authority to contract for 10 years is unprecedented and will require further review. The support clearly signaled a vote of confidence in the program and the recognition that the CIS was an integral, priority program of NCI.

A key factor to winning that support was the program's own track record. The directors of NCI had traditionally supported the CIS, but the institute's division directors had been more skeptical, concerned about inroads into their own budgets and puzzled about the role of a "maverick" communications program in the midst of a research institute. By 1991, a quiet phenomenon had taken place. Over the years, the CIS had become deeply woven into the fabric of NCI programs, evolving into field offices for a variety of national initiatives.

OCC was able to point to CIS efforts that contributed to programs of each research division. These efforts included providing the public with information on cancer risks, such as diethylstilbestrol and asbestos; lifestyle factors, such as smoking and diet; cancer screening and early detection programs; state-of-the-art treatments; and referrals to clinical trials. For the first time, each division director was ready to acknowledge that the CIS played an important role in many of the institute's major programs, including his or her own.

The institute recognized that the CIS could be quickly mobilized to meet a changing public-health need or to launch new NCI initiatives, including those to reach underserved populations. From the mid-1980s, the CIS had been "plugged in" to helping NCI reach its objectives for the year 2000—to reduce cancer mortality—by providing state-of-the-art information on cancer treatment, early detection, and prevention. The CIS had increasingly become an important vehicle for technology transfer—for carrying out the mandates of the National Cancer Act—making the results of research known to the American people.

The cancer-control objectives for the nation, geared to the year 2000, were based on applying current knowledge about the prevention and control of cancer through lifestyle factors, screening, and treatment.

As Vincent T. DeVita, Jr., M.D., then Director of NCI, said:

A reduction in the cancer mortality rate of as much as 50% is possible if current recommendations regarding smoking reduction, diet changes, screening, and state-of-the-art treatment are effectively applied, and if we continue to advance cancer patient survival through improved treatment. . . . It is only through research and the effective translation and communication of research results to practitioners and the public that we can continue our progress (58).

Dr. Samuel Broder, M.D., current Director of NCI, has noted ". . . the CIS is a core function of the Institute." In his 1990 congressional testimony, he said:

Reaching out to all Americans, NCI makes state-of-the-art information available to everyone in the country through the Cancer Information Service (CIS) via its toll-free 1-800-4-CANCER number. Over 500 000 people called CIS last year. Counselors use NCI's computerized Physician Data Query (PDQ), which describes state-of-the-art cancer treatment and available clinical trials. Today's CIS is reaching more states and more people than ever before—and last year, NCI mailed out about 18 million brochures and pamphlets (59).

Growing Outside Support

Support for the CIS had grown outside NCI as well. There were many examples of this support during the early 1990s.

In a joint June 1991 statement, ACS and NCI acknowledged the valuable and complementary roles of their respective public communications systems—the Cancer Response System of ACS and the CIS—in providing the public with cancer information (60).

The media at both the national and local levels increasingly recognized the CIS as a national resource and ran the 800 telephone number for public information. Network news programs saw the CIS number as a way to link its audiences to a credible source of information on cancer.

When television and major newspapers ran stories featuring the early findings on the lymphokine-activated killer cell/interleukin-2 treatment, coupled with the 800 number for information, over 1000 inquiries on the subject were answered in 1 day. NBC's investigative report on the variability in quality of mammograms used the CIS number on its evening news program and more than 10 000 women called in 1 week to get information on approved facilities. A recent campaign to inform women about the NSABP (National Surgical Adjuvant Breast and Bowel Project) Breast Cancer Prevention Trial used the CIS number as one source of information. This resulted in over 6500 inquiries in a 6-day period.

Congressional comments. Public demand and support of the CIS was notably reflected in the Congressional Record in 1989 by both houses:

"One unique resource," noted Sen. Brock Adams, "highlighted in our Committee report, is the Cancer Information Service, which brings the latest and most up-to-date information on cancer prevention, detection, and treatment to the general public. In fact, every day over 1500 inquiries are made to the Cancer Information Service."

"I agree with the Senator," said Sen. Thomas Harkin, "that the Cancer Information Service is a tremendous resource to the Nation and that the NCI should do all that is possible to be sure this program is adequately funded under this appropriation" (61).

"I would like to emphasize," stated Rep. Barbara Vucanovich, "the many vital services provided by the Cancer Information Service. The Cancer Information Service receives more than 400 000 [*sic*] calls every year on the nationwide toll-free phone line, 1-800-4-CANCER. Most of these calls come from cancer patients and the general public, but the Cancer Information Service also provides

up-to-the-minute information on research and referrals for health-care professionals around the country, through the Physician Data Query database. Many cancer deaths could be prevented by early detection, and communications and education are the bridge to improving the odds for early detection. The Cancer Information Service provides the principal public outreach of the National Cancer Institute” (62).

Marilyn Quayle's tribute. Marilyn Tucker Quayle, wife of the former Vice President, paid tribute to the CIS at the program's 15th anniversary in November 1991. In a keynote address to the CIS, she declared her strong support of the CIS in a common battle for life. “We can't allow this disease [cancer] to remain unchecked along a path of pain and suffering. This is the mission of the NCI and CIS . . . and it is, indeed, an urgent one.”

She went on to praise the people who have made the CIS a successful and supportive program. Quayle told staff members of the regional CIS offices that “because of the CIS and because of [your] efforts, we have the power to light tomorrow for our fellow Americans who face this devastating disease. To many, a phone call to the [CIS] can mean the difference between life and death. . . . Through the CIS and their efforts, the dream of a world in which cancer is no longer felt can become a reality” (63).

Foreign CIS programs. The CIS established ties with and began to influence strongly the development of cancer information programs in foreign countries.

Today there are 22 similar services in Europe. At the CIS semiannual national meeting in November 1991, Hilke Stamatiadis-Smidt, director of the Cancer Information Service of Germany, thanked the CIS for its help in building up the German program. In her address, she said:

The model “Cancer Information Service” is a vehicle not to communicate top-down information but to impact science and scientific results in a way adapted to the demands of the general public, at the same time including scientists, clinicians, and doctors in the responsibility for the quality and relevance of the scientific contents. . . . It [the model “Cancer Information Service”] is an American patent with international impact and importance of which we from other countries profit free of charge. Solidarity and cooperation are the pillars an international network of Cancer Information Services will be built on—for the good of the people in the whole world (64).

To the Future

Today, with strong outside relationships and NCI support, the CIS heads toward its new structure and opportunities from a dynamic base. Its track record stands. The CIS has been able to maintain and improve its telephone service, giving high-quality medical information to callers to help patients and their families make complex decisions at a difficult time in their lives; by the end of 1992, more than 5 million calls had been handled. Over 18 million publications are distributed each year. Last year, the CIS made 95 000 referrals to clinical trials and cancer centers.

As an important tool to carry out the institute's messages and programs, the CIS has served as an oasis of fact and balanced perspective in the midst of conflicting and confusing health claims and complex news reports on cancer. Its capacity for immediate response and for translating research progress has remained important (Table 7).

Table 7. Chronology of CIS events—the 1990s

January 1990	Sixth National ACS-NCI Cancer Communications Conference, Washington, D.C.
February 1990	Policies and procedures manual inaugurated
February 1990	Fifth set of 17 CIS contracts awarded
April 1990	Minority Cancer Awareness campaign conducted
July 1990	CD-ROM technology for accessing PDQ installed
September 1990	Prostate Cancer Awareness campaign conducted
October 1990	New outreach staff hired; outreach component restructured; four NCI target audiences designated: African Americans, Hispanics, older Americans, populations with low literacy rates
February 1991	CIS celebrates its 15th anniversary
April 1991	CIS management study completed
April 1991	Minority Cancer Awareness campaign conducted
June 1991	FTS 2000 with advanced telecommunications technology implemented
June 1991	New CIS regional structure proposed
June 1991	ACS and CIS program leaders agree on complementary status of respective toll-free services
August 1991	Breast cancer call guide developed and pilot tested
September 1991	New comprehensive cancer centers guidelines strengthen connection between CIS and centers
January 1992	New national test-call system—the Cancer Information Service Reporting and Evaluation System (CISTERS)—began
January 1992	RFP with final configuration of network released
April 1992	Minority Cancer Awareness campaign conducted
April 1992	CIS used to inform women about NSABP (National Surgical Adjuvant Breast and Bowel Project) Breast Cancer Prevention Trial
April 1993	Sixth set of 19 CIS contracts awarded*

*Nineteen offices now cover the entire country in a reconfiguration of the network.

The CIS continues to be a link between research and practice. In 1992, as NCI turned to new high priorities aimed at major killers—breast, lung, and prostate cancers—the CIS prepared to be a key player in these efforts. Early in the year, the landmark NCI Breast Cancer Prevention Trial, with a recruiting target of 16 000 women, relied on the CIS to triage interested callers to regional investigators.

The role of the CIS will be more significant than ever as it builds sustained networks in its outreach program, involving links to all 50 states, and mobilizes intermediaries to bring health education directly to the people.

Once again, the CIS is in transition. It is in the process of implementing new program concepts. The immediate challenge is the phaseout of the old and adoption of a new, different program structure. With new challenges come new opportunities. The program has never been and will never be static. It moves with the times, evolving to meet changing needs—to be on the front lines of cancer communications, available to all Americans.

The CIS must remain sturdy yet flexible, stable yet progressive to meet the challenges in the field of cancer communications in the 1990s and to have an impact on that challenge. As the CIS successfully implements the new program concept, it will continue to be a template for national and international health communications programs for the 1990s and beyond.

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Effect of the Mass Media in Promoting Calls to the Cancer Information Service

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The Cancer Information Service is a toll-free telephone inquiry service that provides information about cancer and related resources to the public, patients and their families, and health-care providers. The service was created in 1975 to provide rapid access to the latest information about cancer, to address specific population needs, and to bridge gaps between cancer research and application. This article reviews a variety of ways in which the mass media have been used to promote calls to the Cancer Information Service. Conclusions are drawn about the usefulness of media promotion in the past, and recommendations are suggested for future media promotion of the service. [Monogr Natl Cancer Inst 14:35-43, 1993]

INTRODUCTION

For the Cancer Information Service (CIS) to be used effectively, the public first must be aware of its availability. Initially, media promotions of the CIS were broad in scope, designed to accustom the public to using the telephone as a source of information and advice about cancer. Later, promotional strategies became more focused, targeting a specific audience (e.g., cigarette smokers) or a single issue (e.g., cancer prevention). CIS promotions have employed a variety of tactics, including press releases, public service announcements (PSAs), direct mail, and video news releases. In addition to these planned promotions, CIS's name and telephone number have been added, where possible, to cancer-related media stories planned by others (e.g., a "Good Morning America" segment on tobacco use and a *Glamour* magazine article on breast-cancer screening). News stories, particularly those dealing with treatment "breakthroughs" reported in medical journals, have had the most consistently demonstrable impact on the types and numbers of calls to the CIS.

ROLES OF THE MASS MEDIA

The mass media can be used to support the CIS in several ways:

- Raise awareness of the service.
- Remind the public of its availability.
- Increase the chances (through repeated exposure) that individuals will remember the number when they need it.
- Model call behavior (e.g., suggest questions to ask).

- Link cancer news with a source for more information.

- Increase call volume.
- Increase specific types of questions (e.g., how to quit smoking) and callers (e.g., men above age 50) (1). Over the years, planned promotion of the CIS in the mass media has addressed each of these roles.

USE OF THE MASS MEDIA TO ESTABLISH THE CIS IDENTITY

When the first CIS office began operation in February 1976, the communication objective was to make the public aware that the service existed. Not only was the CIS new, but the concept of obtaining information about cancer diagnosis and treatment over the telephone was also foreign to most people, including most physicians.

In October 1975, 4 months before the first CIS office opened, a Publicity and Promotion Task Force was created with representation from the National Cancer Institute (NCI) and CIS offices. The task force's first major recommendation was to make the CIS known within the cancer and health-care communities; the media were listed as an important secondary audience to be informed and educated about the network (2). The first promotional materials created about the CIS featured the theme line: "The Cancer Information Service. The public's link to cancer information" (3). Because the federal government does not purchase media space or time for most purposes, the available options for introducing the CIS were to produce television, radio, and print PSAs and to place news and feature stories about the service.

By 1977, promotion planning began to focus more directly on the importance of the mass media. Sporadic mentions of CIS in regional and national media had demonstrated the dramatic impact of news stories on call and letter volume. For example, one article that appeared in *Parade* magazine on March 28, 1976, criticized the ability of local doctors to treat cancer, identified comprehensive cancer centers as the best place to get the latest cancer treatment, and urged readers to write to NCI to get the name of the nearest such center. The CIS network was just beginning to open regional offices, and NCI handled more than 30 000 letters in the month following the article, as compared with about 800 in the previous month (4). This and similar experiences called attention to the need for a

*See "Notes" section following "References."

system to coordinate media placement efforts and to alert all offices in advance of media exposure.

In addition, NCI produced a variety of publicity materials that were used regionally as CIS offices opened across the country. Most offices, however, were reluctant to publicize their services too broadly until they were confident of their ability to respond.

A number of problems, including the following, related to effective media promotion were encountered during early promotion of the CIS.

- Promotion had to be localized by each of the 17 original CIS offices. Phone numbers and sponsors were different for each, and coverage became available at different times, even within one office's service area.

- The list of 17 regional telephone numbers, plus the number of the national office, made national electronic media promotion difficult and print promotion cumbersome. Telephone technology did not permit the use of a single 800 number and the automatic assignment of callers to the nearest CIS office until the capability became available in 1983.

- Some media markets covered more than one CIS office (e.g., the Minneapolis-St. Paul market covered parts of both the Minnesota and Wisconsin CIS service areas).

To facilitate some national media promotion, a single NCI-sponsored telephone number (answered by an NCI contractor) was used, with calls then triaged manually to the geographically appropriate CIS regional offices.

Based on CIS offices' reporting of excess response capability, the NCI-CIS promotion task force was convened again in 1982 to develop a marketing plan with the goal of increasing the volume of calls. One key strategy was to identify and focus on the target groups most likely to use the service (5). In 1983, the national 1-800-4-CANCER telephone number was established; calls to the national number were automatically switched to the appropriate CIS office. This technological improvement, which greatly simplified national promotion and publicity of the CIS, required a plan to introduce the new telephone number while minimizing the loss of local identities. It also required new policies to coordinate national and local promotional activities.

When the task force next met, in 1984, the 1977 National Plan for Publicity and Promotion was revised. A new policy stated that "... the *primary responsibility* for promotion and publicity activities rests with the local CIS offices" (6). Because the CIS offices had the responsibility for response, they also wanted to retain control over media promotion. The NCI role was defined as supportive, ensuring that guidance and coordination, as well as nationally produced promotion materials to augment local promotional efforts, were provided. In addition, the revised promotion objectives for the CIS included increasing public awareness, maintaining and/or increasing the call volume, and increasing the number of calls from specific target audiences. These objectives reflected differences between CIS offices (e.g., some were at maximum call response levels, and others were not). At this time, the CIS

number also became an integral part of all of NCI's media materials, publications, and promotional activities.

A Publications Ordering Service (POS), added by NCI in 1985, permitted CIS callers to direct-order publications without speaking to a CIS information specialist.

RELATIONSHIP OF MEDIA EXPOSURE TO CALL VOLUME

In the years 1983 through 1991, 1 731 817 calls were received by the CIS, excluding calls to the POS (7).^{*} Of these, at least 778 905 (45%) were attributable to media promotion. Of these calls, 504 578 (65%) were attributed to television. By comparison, about 112 000 calls (14%) were attributed to newspapers, about 110 000 (14%) to magazines and newsletters, and about 52 000 (7%) to radio. PSAs in all media accounted for 141 000 calls (18%) attributed to media promotion, with one television PSA, "Chained Smoker," cited by 68 691 callers (9%). Therefore, although the actual number of CIS calls attributable to media promotion cannot be ascertained because of system restrictions, the strong impact of media exposure on call volume is clear.

Case Studies: Results of Media Promotion

Summarized below are findings from selected NCI evaluation studies that illustrate mass-media influence on CIS calls. These case studies include both planned promotions, such as public service and paid advertising campaigns and collaboration with media events planned by others, and unplanned promotions resulting from news events.

The case studies are necessarily selective in their descriptions. In most cases, planned CIS promotions have included a combination of public service and feature-placement strategies, and a combination of media channels (radio, television, and print).

Media campaign targeting former asbestos workers. In 1978, the NCI conducted a campaign to inform former asbestos workers about the hazards associated with asbestos exposure. Campaign messages urged those at risk to stop smoking cigarettes, consult a physician, seek prompt treatment of respiratory ailments, and call the CIS for additional information. Messages were conveyed nationally through television, radio, magazine, and newspaper PSAs, as well as press releases, augmented locally by media placements (e.g., television programming) that were coordinated with health officials in sites of World War II shipyards. In addition, information was sent to labor,

^{*}Because of restrictions imposed by the U.S. Office of Management and Budget, only one third of all CIS callers can be asked what prompted them to call. Therefore, actual calls resulting from a specific promotion could be up to three times higher than the call volume that can be documented through CIS records. Also, because data are available from only a small proportion of total calls, frequently the quantity of data is too small to permit valid analysis of demographic variables.

aging-oriented, industry, fraternal, service, religious, and paramilitary organizations for distribution, and 40 million "About Asbestos" flyers were sent to Social Security and federal retirement annuity recipients. Asbestos pamphlets were distributed through Social Security offices and supermarkets. All campaign materials, including PSAs, included the CIS telephone numbers.

According to Gallup polls conducted before, during, and after the campaign, there was an increase in the percentage of the public who recalled hearing or seeing anything about asbestos during this period. In addition, the increase in awareness of asbestos after the campaign was greater among manual laborers (24%) than among the general adult population (18%) (8). Despite these positive survey results, there were fewer than 20 000 calls and letters to the CIS requesting information about asbestos exposure during the campaign. One reason for this low level of response may have been the large amount of explicit information contained in the campaign messages; the target audiences may not have needed additional information from the CIS. Significantly, many questions to the CIS dealt with current—not former—asbestos exposure, such as through hair dryers, although the campaign did not address this issue (7).

Prevention campaign targeting the general public. NCI's "Good News" prevention campaign, which began in 1984 and included both television and radio PSAs, was designed to inform the public about positive lifestyle practices they could adopt to reduce their risk of cancer.

An evaluation of the initial campaign PSAs, released in three waves from March 1984 through May 1985, found that they coincided with a dramatic increase in prevention-inquiry calls to the CIS. More than 40 times as many calls for prevention information were made in April 1984 as in February, prior to the PSA release—13 565 calls in April versus 323 calls in February (9). The increase was most dramatic following the release of the first wave of PSAs, but calls roughly doubled following the release of each of the two subsequent waves. Although the first campaign waves were not specifically targeted to African Americans, the increase in calls from this population group mirrored the increase for the population as a whole (9). This was a significant outcome because the CIS call rate from the African American population generally had been lower than from the overall population (7). Also, following the "Good News" promotion, the types of questions asked of the CIS shifted markedly from cancer treatment to cancer prevention (9).

Media promotions targeting "hard-to-reach" populations. The third wave of the cancer-prevention campaign in 1985 specifically targeted African American women and featured singer Aretha Franklin as the television PSA spokesperson. These targeted spots tripled the number of calls to the CIS from African Americans—from 222 in the previous period to 641 (10). In addition, 86% of all callers mentioning the "Aretha" PSA as their source of information were African American (10). Still, the number of calls remained very small. It appeared that, in this case, a PSA

alone was not sufficient to increase calls from African Americans. Later campaigns were more successful and employed other techniques in addition to PSAs.

For example, an evaluation of the 1990 and 1991 National Minority Cancer Awareness Week (NMCaw) campaigns showed that the use of themes and artwork appropriate for African Americans resulted in high "gatekeeper" (e.g., public service managers at television stations) acceptance of the campaign. As a result, these campaigns competed favorably with other public service campaigns for air time. A video news release featuring singer Patti LaBelle, which helped launch the 1991 campaign, was ranked among the top 10 video news releases for the first half of that year. It reached about 35 million people (11). Moreover, the public responded. The California CIS office, for example, typically receives about 9% of its calls from African Americans. During NMCaw in 1991, African Americans accounted for 26% of calls (12).

PSAs targeted to Hispanic audiences have produced limited results. One culturally appropriate Spanish-language television PSA, distributed through the two national Spanish-language television networks in 1989, promoted "Guia para Dejar de Fumar," a self-help smoking-cessation booklet. Use of the PSA alone resulted in a small increase in calls from Spanish-speaking callers (7). This promotion, however, preceded the addition of an automatic CIS system to handle Spanish-language calls, and some CIS offices received calls about the "Guia" but had no Spanish-speaking specialists to respond to them.

Another audience that underutilizes the CIS is men, who normally account for only about 28% of callers (7); however, NCI-supported Prostate Cancer Awareness Week campaigns in 1989 and 1990, which included intense public-relations efforts (mostly targeted to general and sports print media and to network television news and talk shows) and offered free prostate screenings, resulted in tremendous coverage of prostate cancer. As a result, the total number of calls about prostate cancer received in 1 week by the CIS (12 987 calls during the 1989 campaign) was more than it normally received annually on prostate cancer, with an especially strong response from men (7).

Television PSAs targeting cigarette smokers. The Office on Smoking and Health (OSH) of the Centers for Disease Control and NCI have frequently collaborated on campaigns to encourage smoking cessation. OSH produces and distributes motivational PSAs promoting the CIS telephone number, and the CIS provides cessation counseling and referral in response to calls. When OSH compared the months of greatest television exposure of three of these PSAs to CIS call volume, the effect of PSA promotion was apparent. As shown in Fig. 1, during the years 1983–1987 there were three 1-month periods of marked increase in CIS calls; each of these months accounted for more than 20% of the total calls for the respective years (13). These peak months corresponded to the periods of greatest exposure of the OSH-produced spots, as tracked by OSH through Broadcast Advertisers Reports. For one PSA that featured then Surgeon General C. Everett Koop,

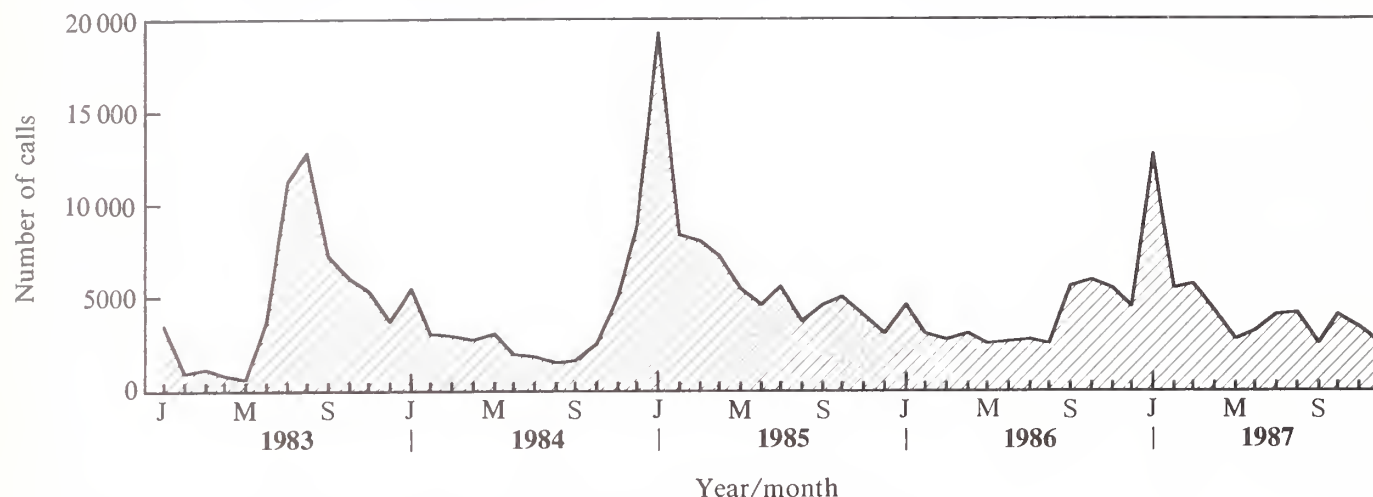


Fig. 1. Monthly frequency of smoking-related calls to the Cancer Information Service, 1983–1987.

the total number of calls from June through September 1983, the time that OSH tracked television airing of the PSA, was 34 900—almost nine times the number of calls during the preceding 4 months (13). Although the increase in calls varied somewhat among the three spots that were tracked, the degree of effect on CIS calls was similar in each case. Also, during these peak call periods, the proportion of calls increased for men, for adults with less than a high-school education, and for adults 40 years or younger. This finding is significant because these are populations that normally call the CIS less frequently than others but that have higher rates of smoking. Other OSH-produced smoking-cessation PSAs that did not specifically refer to the CIS did not result in an increase in CIS call volume.

Radio PSAs targeting young adults. In 1987, NCI produced a series of three radio PSAs featuring Casey Kasem, a nationally known radio personality popular with young adults. Mr. Kasem's mother was a heavy cigarette smoker who died of lung cancer, and he approached NCI to help in an antismoking campaign. One radio spot encouraged young adults not to start smoking or to quit if they had started; two spots encouraged teenagers to help their parents quit. All three concluded with the CIS 800 number, but the major intent of the message was to affect young people's attitudes about cigarette smoking, not to increase calls to the CIS. Further, this youthful audience is not normally a major user of the CIS; less than 8% of CIS callers are under age 20, and only about 19% are aged 20 to 29 (7).

The spots were distributed with a note from Kasem to the approximately 3600 top-40 and young-adult radio stations in the United States. According to an evaluation report commissioned by NCI (14), the spots did appear to receive good play; radio station personnel commented both on the use of Kasem and the quality of production as factors that positively influenced their decisions to air the spots. The spots also appeared to receive more air time during peak traffic hours, when there are more radio

listeners than at other periods. Results showed an increase in calls from younger people (less than 30 years old) during the period when these spots aired; more than 14 000 calls to the CIS were documented (14). This call volume is the highest reported for any CIS radio PSA promotion, although radio PSAs have been distributed routinely in tandem with television PSAs as a part of other campaigns.

Use of paid advertising. Although the federal government in most cases does not purchase media time or space, the comprehensive cancer centers and other institutions can do so on an independent basis. Therefore, it is important to note the results of a study conducted by the Roswell Park Memorial Institute that measured the effect of paid television advertising on CIS call rates. The study compared calls from two groups of similar media markets—paid advertisements were aired in one group of cities but not the other (15). This controlled study specifically targeted women smokers who had young children.

The markets with paid advertising generated nearly 10 times as many calls to the CIS as did the other (control) markets. Also, 31% of all calls received from the test markets were from the target audience, compared with only 18% from the control markets. The number of calls increased dramatically during the times when paid advertisements were aired, with the increase directly related to the amount of time purchased. Overall, about one-half of all calls received from the test markets during the first 28 weeks of the campaign occurred during the 3 weeks that time was purchased. The researchers concluded that purchase of air time markedly affects the number of calls and type of callers. By prorating the cost of air time purchased by call, however, they also estimated that the promotional cost of each new call in this study was about \$61 (15).

Collaboration with a for-profit corporation. During 1984–1988, NCI collaborated with the Kellogg Company to promote the value of eating high-fiber foods to reduce the risks of some kinds of cancer. NCI's health message was delivered in tandem with Kellogg's All-BranTM cereal promotion. The NCI nutrition message, the CIS number,

and an address for obtaining a cancer-prevention booklet appeared on All-BranTM boxes. Television advertising included the NCI message and the CIS number. The Kellogg Company reported that advertising expenditures for the All-BranTM-NCI campaign totaled \$25.9 million for the period 1984-1986 (16).

Pre- and postcampaign surveys of the general public showed an increase in knowledge of the health benefits of fiber. All-BranTM sales increased a dramatic 47%, accompanied by increases in sales of all high-fiber cereals (17). From November 1984 through the end of 1987, nearly 17 000 callers to the CIS reported that they were responding to messages on All-BranTM boxes, and more than 11 000 additional callers said they had seen the CIS number in All-BranTM television advertising. (As previously noted, actual calls resulting from a promotion could be three times the number of calls documented by the CIS.) In addition, more than 34 000 people took NCI's address from the All-BranTM boxes and wrote for free prevention booklets (18).

Mass media and clinical trials. In 1992, NCI instituted the Breast Cancer Prevention Trial (BCPT), a large study to be carried out in 270 hospitals across the United States and Canada. The study needed to recruit 16 000 women at high risk of breast cancer to determine whether the drug tamoxifen could prevent this type of cancer. At an April 1992 national press conference, NCI announced the BCPT and asked women who were interested in participating to call either the CIS or the American Cancer Society's Cancer Response System (1-800-ACS-2345). Many of the 270 participating hospitals held simultaneous news conferences that were covered by local media. This was the first time that a news announcement was used to recruit patients into a specific clinical trial, and it produced a record CIS short-term call volume on a prevention topic: the CIS received more than 6400 calls about the trial within a week of the announcement, and the American Cancer Society received 2700 (19,20). Within a few months, 25 000 women had been screened for possible participation in the trial (7).

Linking the CIS With Planned Events

One strategy for promoting the CIS has been to encourage use of the 800 number by other groups engaging in relevant media activities. Since the inception of the CIS, the NCI Press Office has routinely suggested that national magazines or newspapers preparing cancer-related features include the CIS number so that their readers can call for more information. In 1984, as a typical year, the CIS number was included in articles in *Good Housekeeping*, *U.S. News and World Report*, *The National Enquirer*, *Redbook*, *Self*, *Glamour*, *Better Homes and Gardens*, and *Woman's Day*. The net effect of these linkages has been a constantly increasing, media-driven call volume (7).

Occasionally, this strategy creates a large spike in call volume. In May 1985, Frank Field, a health reporter who appeared on the CBS television affiliate in New York City, narrated a week-long series on diet and cancer during the local evening news. Each night he mentioned NCI's new

booklet, "Diet, Nutrition, and Cancer Prevention: A Guide to Food Choices," and suggested that viewers call the CIS to get a copy. As a result of these five brief segments in one media market, the CIS received 75 000 requests for the booklet (7). The previous high for a television promotion of an NCI booklet had been 18 000 requests for "Clearing the Air," a how-to-quit-smoking guide promoted on ABC-TV's "Good Morning America" for 5 consecutive days (7).

One of the most demanding linkages for the CIS occurred in 1980 when the Public Broadcasting System (PBS) aired "Joan Robinson: One Woman's Story," a powerful 3-hour drama about a woman's 2-year ordeal with terminal ovarian cancer. CIS offices stayed open late the night of the broadcast to be available to callers, and the 800 number was flashed repeatedly on the screen during the program.

The CIS took nearly 3700 calls that night, many of them at PBS stations where CIS staffed phone lines. Because of the wide range of emotional reactions to the Joan Robinson story, it was difficult to categorize caller responses. They ranged from "wonderful" to "gruesome"; many callers said the broadcast had led them to discuss issues they had never openly faced before. Eighty-two percent of the calls were from women. The majority of calls (55%) were from 4 to 10 minutes in length, about double the length of an average CIS call at that time. The type of call, however, was more typical: patient-related inquiries accounted for about 50% of calls (21).

As another example of media linkage, NCI connected in 1990 with the home video licensee of the movie *Glory*. The company agreed to add an NCI television PSA to the opening of the video; the PSA featured entertainer Nancy Wilson advising women to get a mammogram and provided the CIS number. The movie was expected to achieve a home viewing audience of 25 million people. Data relating CIS calls to this promotion are not yet available.

Calls Generated by Cancer News

Since the inception of the CIS, media coverage of cancer news has consistently had the greatest impact on the service's call volume. As noted previously, CIS call records document nearly 779 000 calls generated by the mass media, and only 18% of these, or 141 000 calls, can be attributed to PSAs (7). Unplanned media exposure occurs in two distinct categories: 1) a celebrity, such as a U.S. president or a top actor, is diagnosed with cancer, and the resulting media coverage drives up public interest in a particular type of cancer and 2) research findings published in a medical journal and reported in the popular media lead cancer patients to believe that a treatment "breakthrough" has occurred, causing them frantically to seek out access to the new treatment.

Other types of national news reports on a cancer topic also spur calls, particularly when the topic is negative (e.g., a report that mammography facilities are not accredited) and when the news is carried on a television network.

News of President Reagan's colon cancer. Cancer communicators have long had difficulty in attracting media coverage of colon cancer despite its position as a major cancer killer (22,23). The announcement on July 15, 1985, however, that President Reagan had colon cancer propelled both the public's interest in the disease and the media's willingness to cover it. Before the announcement, the CIS nationwide received only about 50 calls a day about colon cancer. After the announcement, the number of daily calls jumped to 1250 (24).

An analysis of this event found that before the Reagan diagnosis most CIS calls (59.1%) came from cancer patients or their families and friends; in the 20 days after the diagnosis, 68.9% of calls came from the general public (24). Media coverage of the diagnosis also increased the number of first-time users of the CIS, which was mentioned in the news reports. News of Reagan's cancer also generated proportionately more calls from men and older adults. The percentage of colon/rectum-inquiry calls from men increased from 30% before the news to 39% after the news. For people aged 60 or older, the proportion increased from 24% to 38%. Finally, and importantly, news of Reagan's surgery shifted the type of questions received by the CIS. Before the surgery, most callers wanted treatment information or information about local organizations and services; afterward, most callers inquired about general cancer information or prevention.

Four years later, another study (25) found that the increase in public interest in colorectal cancer was followed by a corresponding increase in the use of early-detection tests for the disease. Between 1983 and 1987, use of early-detection tests grew, on average, about 12% a year. In 1985, the year of Reagan's surgery, use grew 28%. The study also found that between 1984 and 1986 the proportion of colorectal cancers detected in early stages increased from less than 37% to more than 40%.

News of interleukin-2. In December 1985, President Reagan's surgeon, who was also chief of surgery at NCI, published a preliminary report in the *New England Journal of Medicine* of the results of a new biological, immune-system-enhancing treatment for cancer known as interleukin-2. The results indicated real gains in some cancer patients who had failed to respond to all other treatments. To avoid raising unrealistic hopes among patients, NCI elected not to hold a press conference about the research report but rather to prepare an "Update" for the press to put the findings in perspective.

Nevertheless, publication of the research findings in such a prestigious journal led to massive media coverage. Two of the three major television networks led the evening news with the story; the third network gave the story second billing. Except for the *New York Times*, all major newspapers carried the story on the front page the next day. The *Times* placed it on an inside page but 1 day later brought it to the front page. Public reaction was overwhelming. Minutes after the network reports aired, the switchboards at NIH were jammed—CIS offices were closed for the evening in the East and Central time zones, and just closing in the West. At 9 PM on the night the story

was breaking, a member of the NCI press staff called the *Washington Post* reporter who had been researching the story that day. The staffer urged the reporter in her story for the morning to emphasize that the treatment was very experimental and not widely available and told the reporter that patient calls already were pouring into the NCI. The resulting *Post* article, read widely by reporters and editors of other media, sparked still more coverage of the public's reaction to the research findings that carried over to a 3rd day and generated another wave of patient calls (26). Telephone lines at NCI were so busy that reporters appeared in person to get information. Television crews showed up in CIS offices to film counselors talking to patients.

Calls to the CIS offices about interleukin-2 reached 1000 a day, and many callers could not get through. Most callers were cancer patients or their families desperately seeking a treatment they thought was their only hope. Unfortunately, CIS staff had to tell these callers that there was no room in the initial study but that there were other treatment options and appropriate clinical research opportunities. About 40% of callers were referred to NCI regional comprehensive cancer centers (27).

An analysis of callers found that those asking about interleukin-2 had demographic characteristics similar to those of patients and family members who call about other topics. It also showed, however, that callers about this new treatment were more likely to have heard of the CIS through the mass media—television (25.2%) and newspapers (14.2%)—than had regular callers (28).

Exposé of mammography facilities. Public alarm created by negative national news reports on a cancer topic is also reflected in CIS calls. Such reports have included a 1981 syndicated *Washington Post* series of articles condemning chemotherapy as an ineffective "killer" treatment (29) and a 1990 "NBC Nightly News" series on the problems with unaccredited mammography facilities (30).

The NBC series exposed problems in a number of facilities providing mammograms, criticizing many facilities as incompetent and alleging misdiagnosis as a common problem. The dramatic impact was heightened by on-camera interviews with women whose cancers had been missed and then found later in advanced stages. The NBC reports came after concerted efforts by NCI and other cancer organizations to increase awareness among women of the importance of mammograms, and they caused public concern and confusion. In the days following these reports, the CIS received nearly 11 000 calls from women who wanted to know what to do, including 3000 in 1 day (7).

CONCLUSIONS

Fifteen years of experience with media promotion of the CIS, typified by the case studies summarized above, allows a number of conclusions to be drawn about the role that the media can play in increasing use of the service.

1) *The mass media produce a demonstrable effect on the number and types of calls to the CIS, as well as on the types of callers.* Calls to the CIS increase when the service is promoted in the media and decrease after a promotion ends. In general, cancer patients and their families are more motivated to call the CIS than other population groups, but promotion of specific kinds of information can increase calls on the publicized topics from the public at large. Similarly, promotion targeted to a particular segment of the population, including groups labeled "hard to reach," can increase calls from that segment; however, the degree to which these targeted promotions are successful varies by the topic, the targeted audience, and the design of the promotion.

2) *The effects of media promotion vary depending on the message, the spokesperson, the media channel, and the targeted public.* One critical factor in ensuring the effectiveness of media promotion is effective planning, which begins with target audience definition. Another crucial factor is whether both media gatekeepers and the target audience will find a specific topic important and relevant. Media planners must then ensure that the message design and spokesperson are both attention getting and appropriate for the topic and target audience and that the media channels selected are those attended to and trusted by the target audience. NCI's experience has demonstrated that many so-called "hard-to-reach" audiences (such as African Americans, young adults, and men) can be reached and will respond to the CIS, if media planning and execution follows these key principles.

3) *An increase in CIS calls depends to a great extent on the intensity of media exposure.* Although evaluations of NCI campaigns have shown that NCI-produced spots usually compete well with other PSAs, a number of recommendations have emerged to help ensure optimal use of PSAs. These include the following guidelines: pair PSA distribution with promotion to station news departments; work with the National Association of Broadcasters (NAB) to distribute spots through NAB's closed-circuit network to member stations; increase promotion with public service directors (or other media gatekeepers); and time PSA releases to take advantage of months when audiences are more likely to be viewing television (especially winter and spring).

4) *The amount of media exposure is directly related to the amount of resources committed to media placement.* PSAs alone, without other kinds of media promotion (such as video and print news releases), in most cases appear to have too limited an effect to support their continued development and distribution as an effective media strategy. Ideally, the most exposure will result from using a mix of PSAs, message and story placement, planned news, and opportunities surrounding unplanned events.

5) *Collaboration with a for-profit corporation (such as the collaboration with Kellogg) is a cost-effective way to promote specific, high-priority cancer topics.* The most effective media promotions include a combination of strategies; this approach also is more costly than relying

on news or PSAs alone. What may seem very expensive to NCI and the CIS offices, however, may be considered of moderate or even low cost to corporations with large advertising and promotion budgets. Many companies may highly value the credibility they gain in collaborating with a leading scientific agency like NCI.

6) *Paid advertising can result in substantial increases in calls.* Unfortunately, paid advertising appears to be prohibitively expensive, both on a cost-per-call basis and to maintain over time, unless private-sector funding sources can be identified. There is also the risk that paid advertising could jeopardize future public service availability for the CIS or even for other nonprofit health organizations. Buying time or space in the media is also complicated, requiring negotiating skills to get the most exposure for the best price, and procedures may vary from locale to locale. Clearly, any decision to commit to the use of paid advertising should be carefully weighed.

7) *In general, television exposure appears to increase calls more than exposure through other media.* With well-placed exposure on television, calls to the CIS can increase dramatically and quickly. Although there is some residual effect after television exposure ends, the volume declines rapidly. In contrast, caller responses to print media placements or other less intrusive promotions (e.g., messages on cereal boxes) are typically lower but may persist longer.

8) *News is the most significant force in increasing call volume.* News about cancer treatment, when prominently featured, produces the greatest increase in calls; as expected, these calls are mostly from cancer patients and their families. News about a celebrity diagnosed with cancer causes predictably large increases in CIS call volume. News about other topics (such as nutrition) may not consistently produce increases in call volume because cancer prevention interest among the public at large may be more fickle than treatment interest among cancer patients.

9) *Effective media promotion that results in calls to the CIS may also lead to other actions.* For some people, the call to the CIS may be only one of several actions taken. Callers may subsequently get a mammogram, stop smoking, enter a clinical trial, or change their cereal preference. Additional research should help identify how CIS calls and media promotions, together or independently, influence subsequent action.

10) *Because media promotion generates calls to the CIS, linking promotion plans with response capabilities is crucial.* It is important to acknowledge the effects of media exposure on CIS calls and to have systems in place to ensure consistently high-quality responses, adequate capacity to meet increased volume, and early warning of all CIS offices about forthcoming media coverage.

11) *The CIS, when adequately promoted, can be a key resource in stimulating interest and action among targeted populations.* Linking media exposure and the CIS can quickly inform an at-risk public, activate an interested individual (e.g., a smoker), and provide access to screening or cancer treatment. Therefore, the use of the mass media and the CIS should be integral components of NCI's cancer-control strategies.

RECOMMENDATIONS FOR FUTURE USE OF MASS MEDIA

Based on the results of past media promotions and anticipated NCI and CIS priorities and capacities, the following recommendations are offered for using the mass media to promote the CIS.

1) Promotion must be carefully *planned*, with close coordination between promotion activities and CIS response capabilities. Unmanaged media promotion can jeopardize a system such as the CIS if the system is not prepared to respond to volume (e.g., with sufficient copies of materials) or type of service requested (e.g., Spanish-language calls).

2) A national promotion task force and a national promotion plan are pivotal in ensuring strategic use of the media as well as adequate response by the CIS. Throughout the CIS history, these mechanisms have allowed for consideration of the needs of all CIS offices and for periodic reassessment of the respective roles of NCI and the CIS in national and regional promotions. Therefore, the national promotion task force should be maintained and a national promotion plan developed.

3) Media promotion should include a broad mix of promotion and publicity strategies to take advantage of the benefits of each and to overcome the limitations of any one approach.

4) For a national telephone response service constructed like the CIS, nationally planned and produced media promotion is more efficient and successful than decentralized promotions shared among regional offices and should be maintained. National media contacts are nurtured through NCI; planning and production achieve economies of scale; and a "quick alert" system from NCI to each CIS office improves overall response. Locally originated media promotion, however, also has a role when an issue or opportunity is identified locally and can be contained within one media market.

5) Promotion of the CIS should be tied into broader programs rather than marketing the CIS as a stand-alone service. Effective program tie-ins give the target population a specific topic to respond to, further the aims of the overall program, and integrate the costs of CIS promotion into broader program budgets.

6) Paid advertising is expensive to sustain and should not be considered as an alternative to other media promotions except where there is an immediate, short-term, high-priority need or when a corporate sponsor can be identified.

7) Placement of messages in the media is highly competitive, time consuming, and expensive. Therefore, the most cost-efficient media promotions are those in which the CIS can be added to a promotion planned by another sponsor (such as a television station) or to a news event. The topic and target audience for a news or other media event, however, must be consistent with NCI-CIS priorities; otherwise, limited CIS response capabilities will be consumed by calls that do not address the most critical program needs.

8) For some types of messages and callers, the CIS may not be the most appropriate response strategy. Some cancer-related messages may be completely delivered to the public without the need for a follow-up call, or a call may be more efficiently placed to an end point other than the CIS (e.g., directly to a physician). Where a person in a particular population segment is unlikely to use the telephone to ask for information, it may be more effective to direct that individual to a more comfortable information source rather than to try to change his or her information-seeking behavior.

9) Ongoing media outreach and nourishing of relationships with journalists and other media gatekeepers are essential to minimizing inaccurate, unwanted, or potentially misleading publicity. Although the CIS is an invaluable resource for the cancer community in responding to unplanned media events, such coverage may have long-term negative results and cause a shift of resources away from established priorities to handle crisis calls.

10) NCI should continue to explore technological advances to increase the capacity of CIS offices to respond to the public. Increasing the efficiency and effectiveness of CIS response systems is a prerequisite for improvements in media promotions to increase CIS call volume.

11) Additional research would be useful in determining more precisely how the mass media can be used to reach targeted populations and increase their use of the CIS. Other research needs include the following:

- A broader examination of the cost-effectiveness of paid advertising to motivate specific, targeted audiences to call the CIS.
- An examination of the extent to which behavior change is triggered by combining media promotion with a CIS response mechanism.
- Additional exploration of the use of radio to promote calls from audiences that may be more effectively targeted through this medium than through television.
- A refinement of the kinds and extent of CIS caller data collected, a more thorough analysis of who is calling to assess whether the most crucial target audiences are responding, and more complete analysis linking types of media exposure to specific types of caller response to help direct future media promotion plans.

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Outreach Programs and Their Effects Within the Cancer Information Service Network

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Outreach programs have been part of the Cancer Information Service (CIS) program since its outset. The scope of work of the first two CIS contracts gave broad responsibilities to the local offices for public and professional education, responsibilities that were carried out in a diverse fashion with little national direction. As the National Cancer Institute (NCI) Office of Cancer Communications matured and became more directed, the CIS local offices began successfully to implement programs with the Office of Cancer Communications and through intermediary groups. The Partners in Prevention (PIP) effort, launched by NCI in 1984, was the first major national community education program in which all the CIS offices participated. Shortly after the inception of PIP, however, the outreach personnel were deleted from the CIS contracts, due to budget restrictions. When the outreach component was reinstituted in 1990, the structure of the program changed to a catalytic role, working with local media and intermediary organizations to bring the NCI program messages and materials to targeted audiences and memberships. Under the reconfigured CIS network, the outreach program will serve as a resource to both those community institutions that are funded by NCI and those that are not and will be proactive in intermediary development. This paper details the chronology of the program and presents some of the research issues that need to be addressed in the future. [Monogr Natl Cancer Inst 14:45-59, 1993]

Early in the planning for the Cancer Information Service (CIS), the National Cancer Institute (NCI) staff recognized that telephone service was only one aspect of the CIS. Clearly, an outreach component that was to grow in parallel with the telephone service was also the intent (1). Both public and professional audiences were key targets in NCI's plans.

This article will cover the development of the CIS outreach program and its evolution from local initiatives begun in 1975 to the intermediary model based on the national priorities of the 1990s. It will describe some of the barriers encountered in designing and implementing a national outreach component, including the funding cutbacks that have plagued the program throughout its existence. In addition, the article will discuss five of the programs that were initiated as a result of the Partners in Prevention (PIP) campaign and will discuss four nationally funded initiatives focused on African Americans. Future opportunities, evaluation needs, and research efforts will also be delineated.

BACKGROUND OF OUTREACH IN THE CIS

When the original contracts were issued in 1975 to the 17 comprehensive cancer centers, they required that the CIS conduct public education and professional education programs.

In the area of *public education*, the target audiences were to be determined by the needs of the local offices in consultation with the NCI project officers (2). The scope of work stated that the local offices would make every effort to plan and conduct the public education program in cooperation with other agencies and organizations concerned with cancer. It listed the types of efforts to be included:

- 1) Collaborative programs to provide cancer information through employee and trade organizations, unions, churches, fraternal organizations, consumer and patient organizations, health centers, hospitals, and other community settings to ensure maximum exposure of the program to target audiences.

- 2) Collaborative programs to formulate cancer-education programs for primary and secondary schools, colleges, and universities where needed.

- 3) Working relationships developed with the media to stimulate newspaper, radio, and television use of pertinent cancer-related information.

- 4) Cooperation with other cancer outreach programs, agencies, and organizations to publicize and promote the use of screening projects and other facilities by target audiences.

- 5) The establishment and promotion of a service to provide volunteer speakers to community groups.

In the area of *professional education*, the local offices were told to make every effort to cooperate with other agencies and organizations concerned with cancer. The CIS offices were to work with the region's professional groups, center consortium group members, the American Cancer Society (ACS), and NCI-funded networks and projects to provide information and services to health professionals (especially those dealing with target audiences); and to publish and distribute, or work with other organizations that publish, a quarterly newsletter for the region's health professionals to keep them informed

*See "Notes" section following "References."

about cancer-related activities, services, and materials available.

In addition, the offices were required to provide the following on request to health professionals:

1) Access to a resource center where they could obtain information on national, state, and local programs, services, agencies, organizations, and health institutions concerned with cancer.

2) Easy and economical access to cancer center expertise in cancer, including access to the latest diagnostic and patient-management information and access to consultation for immediate patient-management problems.

3) A channel of communications to relay their needs to the cancer center.

The original policies for operating the CIS, set forth by NCI in 1976, also addressed the planning of professional and public information and education activities. A public and professional education committee consisting of NCI, ACS, and comprehensive cancer center personnel was established to identify gaps in existing information/education activities. The CIS network offices were asked to support existing public and professional information and education programs within their area of service. The purpose was to further the reach and to increase the impact of those programs, with highest priority to be given to the establishment of programs to reach professional and public audiences not currently benefiting from existing programs. Those audiences were to be identified and reached in cooperation with the ACS and other cancer-concerned organizations and institutions (3).

By the time of the national CIS meeting in Miami in 1976, the national media plan noted that

the media program will acknowledge that . . . CIS is now, and will increasingly be in the future, more than a telephone response system. Cancer education programs tailored for target audiences are in the initial stages of development and will claim an increasing share of program activities. However, it must be recognized and expected that the telephone service will continue to receive the greatest attention from the media for the foreseeable future. As other programs are developed and implemented and show results, the latter will also receive publicity (4).

In addition, the report of the Evaluation Task Force, also presented at that meeting, outlined methods for community needs assessments to identify target populations as well as methods for pretesting materials and evaluating programs.

Center Characteristics Added

NCI added two new characteristics in 1976 to the requirements made of comprehensive cancer centers. One required centers to provide evidence of resources and plans for effectively communicating results of research and demonstration activities. The second required centers to coordinate efforts with other programs in the community through the Health Systems Agencies. In November

1976, the NCI described the outreach activities of the CIS offices in relation to this change and noted: "Each center must determine the needs of the community it serves and designate target groups and programs it wishes to work on" (5). NCI gave some 30 examples of activities that might be undertaken with three target categories: health professionals, cancer patients, and the general public. The activities ranged from developing educational programs for hospital workers to establishing newspaper columns to developing programs for minorities and rural extension agents. Several offices had already begun outreach programs, including newsletters for professionals, newspaper columns for the public, rural outreach programs, patient/family education programs, a nurse-to-nurse referral service, and columns for a medical journal. The activities were diverse and were run successfully in each local area. They made little national impact, however, because although they were based on the requirements of the contract, there was no cohesion, no feeling of network, and little direction from the national level. The limited staff available at the local CIS offices was concentrated mainly on the opening of the telephone service—a much more labor-intensive task than had been anticipated when the contracts were originally written.

Merit Review Recommendations

When NCI's Division of Cancer Control and Rehabilitation (DCCR) conducted a merit review to evaluate the first 3 years of operation of the CIS in 1978, it noted several strengths of the program and the following barriers facing the outreach component:

- The difficulty of separating CIS from the other cancer-control activities within the cancer center and/or other cooperating cancer-related agencies.
- Limited access to information for allied health professionals.
- Insufficient plans to identify and reach specific target audiences (6).

CIS OUTREACH ROLE IN THE 1978 RENEWAL CONTRACTS

The evaluation of the merit review team was reflected in the renewed contracts issued in 1978, in which the responsibilities for public information and education programs and for programs for allied health professionals were delineated (7).

For public information/education programs, the responsibilities included assessing the needs of the various audiences and working with appropriate cancer-concerned organizations in the development and implementation of programs targeting at-risk audiences in the cancer center's geographic area. The programs were to be conducted in cooperation with other concerned agencies and organizations.

The CIS was responsible for setting up displays of cancer-related materials and publications at meetings of health professionals, at health fairs, and at other places

where such displays were deemed appropriate and feasible and for maintaining a roster of speakers for use at various functions and with various groups. The CIS was to identify cancer patient information/education needs and develop materials and programs to meet those needs, pretesting the materials developed when feasible through available sources. The materials and programs developed were to be publicized for use at hospitals and by interested organizations and institutions.

In addition, there were duties to be carried out in the area of continuing professional cancer information/education. Cooperating with other cancer-concerned agencies and organizations, the emphasis was to be placed on programs for nurses and other allied health professionals based on demonstrated needs. Programs for physicians, however, were "not excluded nor deemed inappropriate." The production and distribution of current publications geared to the region's health professionals were to be continued, and new publications could be started if there was a demonstrated need.

Minority Activities

New outreach activities generated among the CIS network offices included national task forces on African Americans and on Hispanics. Several offices serving areas with concentrated minority populations—Memorial Sloan-Kettering, M. D. Anderson, University of Southern California, and University of Miami—aimed outreach efforts to these target groups.

All the local CIS offices had forged strong relationships with other cancer-related groups and were running programs in close collaboration. The many accomplishments in the outreach area were especially noteworthy because most offices had only one half-time to full-time outreach person carrying out the program. Again, the broad description of outreach activities resulted in a multitude of programs, many of which were of merit but had little relationship either one to another or to the national program as a whole.

Special Projects

As a result, NCI had developed by 1980 a specified format for approval of outreach projects—now called "special projects." It included a description of the selection of the project delineating other cooperating groups, problem analyses, goals, program methodology, implementation steps, and evaluation criteria.

CIS AND THE OFFICE OF CANCER COMMUNICATIONS (OCC)

The NCI Office of Cancer Communications, with an augmented staff, also began in the late 1970s to lead the CIS with programs based on national priorities and national research.

OCC was implementing the concept of using intermediaries—access groups, including the media—that could

reach the public and individual health professionals with NCI messages. Instead of communicating directly with final target audiences, the intermediary approach supports and motivates groups that can directly address the public, patients, and health professionals. In working with intermediaries, OCC would determine project areas, select the primary target audiences, determine appropriate messages and suggested communications channels, and produce materials and programs.

OCC felt there were several reasons for working with intermediaries. Intermediaries could help by providing access to a target audience, giving additional credibility to NCI programs and messages, furnishing added resources and expertise, and supplying program cosponsorship (8).

But OCC's implementation of the intermediaries model was a prelude to a dilemma that would plague the CIS outreach program for many years. From the start, the outreach portion of the CIS program was the most ambiguous. In addition, the programs of the NCI's DCCR and OCC were changing; both entities were becoming stronger. OCC embraced the CIS as its field offices, relying on the CIS for interfacing with its various publics at the local level. On the other hand, as the DCCR moved from its original community-based programs into cancer-control research, it did not factor the CIS into its research initiatives. Instead, as the years progressed, the division moved closer to funding state health departments as its outreach arm.

These changes created a paradox—the CIS outreach program was being judged in terms of cancer-control research, while its contract mandates and its activities were being directed into the social marketing and intermediary arenas. As a result, the CIS outreach program in its early years suffered from dual leadership at the national level, a hindrance that was compounded by a lack of definitive outreach goals based on national priorities and an inadequate staff at the local level.

EARLY OCC-LED PROGRAMS

At the 1980 CIS national meeting in Madison, Wisconsin, OCC presented a breast self-examination initiative. This major communications initiative was based on findings from a national survey, conducted by OCC in 1979, to measure public knowledge, attitudes, and practices related to breast cancer. The initiative would include regional workshops, educational materials for both the public and patients, and kits for reaching intermediaries, including breast self-examination programs geared to hospitals, nurses, and office physicians.

In the early 1980s, OCC also began planning for a major cancer-prevention program that ultimately became a part of NCI's effort to reduce the cancer mortality rate by the year 2000 to 50% of the 1980 rate. OCC was eager to have the CIS as a partner in this effort and enlisted the help of its Publicity and Promotion Task Force.

Its rationale for involvement of the CIS network was noted in a memo to the task force:

One of the major objectives of the network is to increase public awareness of the importance of cancer prevention. The network's credibility, informational resources, staff experience with public awareness campaigns, and explicitly stated interest in promoting cancer prevention render it the most important and potentially most effective intermediary in the OCC cancer prevention program. CIS involvement is considered essential to the successful implementation of this initiative on the local level (9).

The network would also benefit from participation in the prevention program. All materials produced for this program by OCC would promote the CIS toll-free number, 1-800-4-CANCER, which would result in increased public awareness and use of the CIS. In addition, the national focus on cancer prevention would provide local offices with a major theme around which future special projects could be organized.

The program was carried out in two phases. Phase I was to create broad public awareness of cancer risk factors and prevention behaviors. Initially, the program would provide the public with general information on cancer and its prevention, primarily through the mass media. Phase II, to be launched during the summer of 1984, would shift the program emphasis from informing the general public about cancer prevention to encouraging behavior change in populations at higher risk for cancer. Organizations serving the target groups, especially at state and local levels, would be encouraged to develop cooperative cancer-prevention programs. Phase II activities included establishing a planning group for each risk factor, target audience, and setting (such as work sites and schools). Each group, in turn, would develop a plan of strategies and activities for its area of concern.

CIS Activities

Five roles were identified for the local CIS offices during phase I of the prevention program: 1) distribution of OCC-produced public service announcements (PSAs); 2) response to public inquiries; 3) stimulation of media activities; 4) cooperation with community organizations; and 5) support for health professionals. Examples of specific projects and activities that could be undertaken by the CIS offices during the first phase of the prevention initiatives were outlined (9).

All CIS offices participated in phase I of the program, aiding NCI in distributing the PSAs, in stimulating media activities, in working on conferences for and materials distribution to health professionals, and in responding to public requests.

Partners in Prevention (PIP) Workshops

Following phase I, a series of seven regional planning workshops called Partners in Prevention were held to inspire the development and organization of local programs to identify priorities for future programming and to serve as a transition to phase II.

Developed and planned by NCI and the local CIS offices, these meetings were held during May and June of 1984. The PIP workshops brought together OCC and CIS personnel and representatives of state and local health departments, ACS and other voluntary health associations, educational groups, business, and many other organizations. These workshops identified specific community cancer-prevention needs and provided the skills essential for meeting those needs.

During lecture and discussion periods and informal small-group sessions on individual topics, participants considered potential opportunities to work together and learned about the assistance that NCI and the CIS offices could provide. The PIP workshops had the following specific objectives:

- To introduce NCI and its Cancer Prevention Awareness Program to health educators and community health program planners.
- To lay the groundwork for the continued diffusion of cancer-prevention messages to target audiences through local intermediaries.
- To encourage independent community cancer-prevention education programming.
- To increase public awareness of the CIS offices as information sources.
- To determine the tools needed by local officials and planners to implement activities (10).

Over the months following the PIP workshops, the CIS began implementing the phase II activities, helping attendees form regional PIP groups, which were to hold meetings and pursue a wide range of activities. The PIP program was the first major national community-education program in which every CIS office participated—each tailoring programs to its specific needs and locations. Some formed formal structures with their workshop participants. Some worked in schools; others went to work sites. Most had a newsletter or some means of communicating with their coalition members. Unfortunately, shortly after the start of phase II activities, NCI's Division of Cancer Prevention and Control (DCPC, a renamed DCCR) cut the outreach personnel from the CIS contracts, due to budget restrictions, and OCC lost the field arm that was to coordinate the regional programs.

NCI studied five of the PIP incipient programs in depth—those at the CIS offices in Boston, New York City, Miami, Colorado Springs, and Detroit—in an attempt to catalog the range of cancer-prevention activities in which the various community-level organizations were involved, to describe how the organizations interacted with one another, and to identify factors associated with relatively active community-prevention programs.

The results of the programs in the first four offices were provided in one study (10); the Detroit program was analyzed separately (11).

Boston, New York City, Miami, and Colorado Springs Programs

The first study found that the range of activities of the regional PIP groups was particularly significant, consider-

ing that all four of these CIS offices stated that, before the PIP workshops, their involvement in cancer-prevention activities had been very limited. In three of four cases, formal written plans were prepared. Target audiences identified in the plans included young people, the African American community, non-English-speaking communities, smokers and other tobacco users, women, persons in high-risk geographic regions, persons below the poverty line, the elderly, and the community as a whole. Risk factors addressed were tobacco use, alcohol consumption, diet, sun exposure, and environmental hazards. Several settings for cancer-prevention efforts were incorporated in these plans as well, including work sites, schools, health clinics, and the home.

Several communication channels and strategies were considered and developed to varying degrees. These channels included direct communication with the public via newsletters, PSAs, broadcast news features, articles in the public press, seminars, and presentations. Indirect means of communication with the public were also used. For example, a newsletter to health professionals was developed by the Colorado Springs CIS, the Colorado Division of ACS, and the Colorado Department of Health; and a major meeting for employers was sponsored by the New York City PIP Coalition. A number of conferences and other meetings were held as a result of the efforts of the PIP groups.

The CIS offices invariably were viewed as the focal point for initiating meetings, organizing and distributing planning documents, and conducting other strategic activities. When the CIS was unable to serve as such a focal point (because of staff unavailability or other priorities), the follow-up needed to maintain overall momentum usually was not available. Once opportunities for new initiatives were identified, however, groups other than the CIS office sometimes assumed a lead role. For example, a PIP member from a community hospital coordinated an effort to begin cancer-prevention seminars in an automobile plant.

Most cancer-prevention activities that were proposed, planned, attempted, initiated, or modified by the four CIS offices and organizations within their regions resulted from the PIP program. The initial regional workshops provided a formal organization, an increased awareness by the participants of each other's resources, and the momentum for actually implementing a significant number of activities.

As a result of these experiences, a number of key conditions were identified as important to implementing cancer-prevention activities by these groups. The presence of these conditions was viewed as a facilitating factor, and their absence was seen as a barrier to either initiating or expanding prevention activities. These conditions are summarized as follows.

1) *Continuing involvement and commitment of CIS staff.* The involvement of CIS staff members was vital to the success of individual activities. Although this did not guarantee the success of a prevention activity, the presence of CIS staff members as coordinators, participants, or

even simply as information resources was essential. Without such involvement, an activity was unlikely to continue. Although CIS offices did not have the resources to maintain a major role in a large number of cooperative activities, their continuous involvement in more supportive roles was essential to maintain momentum.

2) *Clarification of objectives and relative responsibilities in the PIP network.* Although the PIP workshops were used to describe the PIP objectives, several PIP partners felt that the objectives and relative responsibilities needed to be clarified or restated because of the passage of time and the introduction of new groups. Individual CIS offices needed to provide continuing clarification and refinement of the direction of this program.

3) *Expert technical assistance.* Technical assistance from NCI was viewed as having facilitated the development of the regional PIP groups. Future participation by NCI in the groups' efforts, as time and resources permit, was seen to contribute significantly to facilitating the groups' development.

In summary, the PIP workshops served as a catalyst for a number of cancer-prevention activities. They provided an important forum for the exchange of ideas on cancer prevention. Collaboration among regional organizations was often initiated or strengthened. Valuable recommendations that led to new OCC publications and activities were made. Innovations in local cancer-prevention programming were inspired through decentralized program planning and development. Prevention partnerships emerged as a vital short-term approach for disease prevention efforts.

Detroit Program for African Americans

Because African Americans have higher rates of cancer and are more likely to die from cancer than are Whites, OCC targeted the African American audiences as one of its first initiatives in implementing phase II prevention program plans. A national advisory committee was established to help launch and direct the program for African Americans, which involved the following:

1) A nationwide media campaign featuring African American celebrities and leaders promoting cancer-prevention awareness messages on radio and television.

2) Organization of a national "Joint Health Venture" involving a long-range collaborative effort between NCI and leaders of major African American national organizations to stimulate and provide support for cancer-reduction activities in the African American population.

3) Promotion of prevention information within local communities through a "spotlighting" approach, focusing on selected communities with a large African American population and strong community leadership and involvement.

The Cancer Prevention Awareness Program for Black Americans was launched nationally via a press conference and luncheon in Detroit in May 1985. Along with the commitment to serve as the site for the national kickoff activities, Detroit's African American community leaders agreed to initiate a model local media and education pro-

gram in conjunction with NCI's Cancer Prevention Awareness Program for Black Americans. By the conclusion of the national kickoff activities, which included a local seminar for health program staff and professional society representatives, an important coalition of community representatives had assembled, launching Detroit's own local joint health venture as well. Detroit formed a Steering Committee of 60 community leaders and became the first of several selected "spotlight" communities to organize a local effort as part of NCI's Cancer Prevention Awareness Program for Black Americans (similar efforts were initiated in Atlanta, Georgia; Washington, D.C.; and North Carolina).

The Detroit experience provided an excellent example of community involvement around a pertinent health issue—cancer prevention in that city's African American community. Health professionals as well as representatives of organizations, business, religious groups, and the media shared their resources in support of this effort. These program planners designed and implemented outreach activities that reflected the real needs of their target audience.

Elimination of Outreach Staff

As these five programs illustrate, the PIP program was a well-planned and well-executed effort. OCC had deeply involved and energized the CIS network and had spent 2 years in the planning phase working closely with the CIS task forces and committees to undertake this major effort. The implementation of phase II and the entire Detroit initiative were in their early stages when the DCPC, for budget reasons, cut the outreach positions out of the newly negotiated CIS contracts. This severely restricted the efforts that the local offices could make on behalf of the prevention program. Although the program continued, its potential was never reached because of the loss of the CIS outreach staff—the major local catalysts for the program.

ADVENT OF MASTER AGREEMENT ORDERS (MAOs)

To fill the void left by the loss of the local CIS outreach staff, OCC in 1987 issued a Request for Proposals for a series of Master Agreement Orders. These contractual agreements between NCI and CIS offices (or, in some cases, Cancer-Control Programs) would support projects that amplified specific NCI activities at the regional or local levels or that were new, innovative efforts supporting the overall direction of NCI. The Master Agreement Orders covered the following (12):

- Development of education/information program plans that matched national objectives to local efforts.
- Identification of local organizations having established credibility with significant portions of the target audiences and development of approaches to work with such groups in a community project.

- Assistance to NCI to pretest proposed concepts and prototype messages.

- Assistance to NCI in the assessment of existing program materials, campaigns, or other efforts.

- Provision of packaged materials for local media outlets in accordance with OCC specifications.

- Design of a plan to ensure full-scale promotion of NCI materials through the local media and/or other appropriate intermediary groups.

- Pilot test of patient education materials in a clinical setting.

One group of Master Agreement Orders—those concentrating on disseminating cancer-prevention awareness messages to the African American population—will be discussed in this article. Two of these agreements concentrated on reaching African Americans through churches, one used allied health professionals as intermediaries, and one used a self-help community organization dedicated to eliminating "physical and spiritual hunger" through community participation (Table 1). All had evaluation mechanisms built into the program to measure effectiveness of the projects.

Church-Related Programs

The church-related program of the Michigan Cancer Foundation sought to identify a minimum of 50 African American churches in Detroit with the cooperation of the governing body of each denomination and with the assistance of the Metropolitan Detroit Steering Committee (originally set up as part of the PIP program [11]) and sought to present programs on cancer prevention at each of the 50 churches. A major media component was also part of the Detroit effort. The program at the Fox Chase Cancer Center, run in cooperation with the Philadelphia Division of ACS, worked with the Conferences of African American Clergy.

The Detroit program reached 24 church congregations, attracting 566 persons. Another 75 persons were reached through demonstrations at churches that did not schedule formal presentations. A total of 520 women and 121 men attended all the Detroit programs. Ten churches requested additional programs. The media portion was basically an extension of the groundwork laid 4 years earlier, using the same outlets to promote the church projects. Seven inquiries for programs came from the media effort (13).

The Fox Chase program made formal presentations to five conferences and one lay association, with 26 churches signing up for presentations as a result of the conferences. An additional 18 churches and four community centers became involved independent of the conferences. A total of 217 persons completed the evaluations, with 95% finding the programs useful and 83% interested in receiving additional programs (14). (Fox Chase used this effort as one of its first steps toward building a cancer-control research program aimed at African American smokers [15].)

Both programs faced many barriers:

- The lack of response from many ministers, lay leaders, conferences, and churches.

Table 1. Summary of Master Agreement Orders concentrating on African Americans

Cancer center	Target group	Program objectives	Program highlights	Barriers encountered
Michigan Cancer Foundation	Churches	Identify minimum of 50 churches in Detroit and, working with the Metropolitan Detroit Steering Committee, present programs on cancer prevention. Develop media component.	Twenty-four church congregations reached—total of 520 women and 121 men. Ten churches requested additional programs. Media effort promoted church projects; seven inquiries for program received.	Lack of response from ministers and lay leaders for scheduling programs; intensive staff effort required. Stiff competition for programs in African American churches. Lack of recognition of cancer as a top priority. Lack of summertime church activities. Low staff morale as result.
Fox Chase Cancer Center	Churches	In cooperation with the Philadelphia Division of the ACS, work with the Conferences of African American Clergy to build program to be carried out by church organizations.	Formal presentations made to five conferences and one lay association; 26 churches signed up for programs as a result. Additional 18 churches and four community centers involved; 217 persons completed evaluations; 95% found programs useful and 83% interested in receiving additional programs.	Lack of responsiveness from conferences and churches. Intensive staff effort required. Gatekeeper role of clergy in protecting congregation from outsiders. Pervasive fear of and reluctance to relate to topic and reality of cancer.
M. D. Anderson Cancer Center	Allied health professionals	Train nurses at city clinics to educate patients about cancer prevention. Use media to broaden target audience's access to cancer-prevention information and to build credibility within target community.	Three city health clinics in predominantly African American, economically depressed neighborhoods selected for intervention; 32 members of City of Houston Health and Human Services Department were trained to conduct 3-minute intervention with each patient, stressing low-fat, high-fiber foods and smoking cessation. Intervention delivered to 14 400 persons at three sites; 4600 quick contest entries submitted by clinic clients.	Proposal-stage planning was insufficient. Prevention intervention put on hold because of summer vacation schedules. Media sponsors not agreeable to plans originally proposed. Project unable to obtain donated billboard ad space for antismoking messages.
Memorial Sloan-Kettering Cancer Center	Community organizations	Use existing coalition of community organization (SHARE Harlem Health Project) to disseminate cancer-prevention awareness messages to African American population. Conduct focus groups to get information to adapt educational information.	NCI dietary recommendations were linked with the food items that are usually purchased by members of community organization. Two information pieces adapted 1) food-information recipe cards linking dietary modification and food preparation messages with the specific foods purchased and 2) a series of "how-to" manuals designed to provide tools and materials for implementing intervention. Combination picture, recipe card, and help tip developed; focus groups tested prototypes. Feedback from focus groups and telephone surveys used to evaluate project.	Limited access to health promotion messages and materials developed specifically to meet information needs to low-income minority populations. Inadequate knowledge and interest among African Americans concerning cancer risk-reduction behaviors. Inadequate knowledge and concerns about risks of developing cancers and about efficacy of early detection and treatment and limited access to mammography screening.

- The competition for programs in the African American churches. Every health agency and program wanted to use churches, especially the large churches, for presentations.

- Failure to consider cancer a top priority. Church representatives also felt that presentations would be too scientific and hard to understand.

- Lack of summertime church activities. Few churches were actively scheduling summer activities.

- Pervasive fear of and reluctance to relate to the topic and reality of cancer.

Health Professional-Related Program

The M. D. Anderson Cancer Center Program, "Alive and Aware," had a clinic-based component to train nurses at city clinics to educate patients within the African American community about cancer prevention. A media-based intervention followed to broaden the target audience's access to cancer-prevention information while providing additional reinforcement and credibility within the targeted community (16). Although project accomplishments were difficult to measure, due to limitations in resources and time, the majority of the project goals were achieved.

Self-Help Community Organization

The Memorial Sloan-Kettering Cancer Center used a coalition of community organizations under its MAO to disseminate cancer-prevention awareness messages to the African American population of Harlem, in New York City. The coalition of Harlem community organizations, entitled the Self Help and Resource Exchange (SHARE) Harlem Health Project (SHHP) had been initiated with the support of a 2-year grant from the Office of Minority Health (17).

The project provided NCI with a unique opportunity to develop and test innovative cancer-communication interventions targeted to low-income African Americans, within the framework of a previously funded cancer-prevention and control-intervention trial. Two specific local adaptations were 1) food-information recipe cards linking dietary modification and food preparation messages with the specific foods purchased by SHHP members and 2) a series of "how-to" manuals for community organizations participating in SHARE/New York designed to provide them with the tools and materials needed to implement realistic and feasible community-based cancer-prevention programs and control interventions.

Implications for Future Outreach Activities for African Americans

The projects described in this group of agreements had some clear successes. They also encountered many barriers. There are, however, some lessons that have been learned from these programs that the NCI staff has used in planning subsequent outreach activities:

- 1) The mechanism of a 1-year MAO with a low level of financial support is not ideal for planning and conducting

outreach programs. A longer project period is needed to allow for a more appropriate planning process, a less hurried and more thorough project implementation phase, and an evaluation process worthy of the financial expenditure. A half-time project coordinator is not sufficient for such a labor-intensive project.

- 2) Building a base in the community of key leadership that will be able to give advice and entry into settings for such programs is essential. If the site chosen is churches, planners must be mindful of the number of conflicts and multiple requests a church receives; focusing on small storefront churches that are often looking for members can be a successful tactic. Giving programs to the congregation as a whole is ideal but difficult to achieve. Presentations to subgroups within the church, such as choirs, nurses' guilds, women's day committees, singles' clubs, senior groups, prayer committees, and missionary societies, should be considered.

- 3) Clear recognition that the program is a labor-intensive effort is necessary, given the state of the problem, the lack of existing organizational infrastructure in the community, the high levels of fear regarding cancer, the mistrust of contractors (especially if previous contact with the community is limited), and the lack of cohesion between the cancer center's institutional mission, defined primarily as research, and the community outreach education programs, defined primarily as service.

- 4) Utilization of NCI's resources is key, because NCI staff has knowledge, experience, and a great deal of materials available.

RESTRUCTURING THE OUTREACH PROGRAM

The movement of the CIS into OCC in 1988 created new program unity, with opportunities to forge an integral role for the CIS in the planning of educational programs targeting national priorities (Table 2). The 1990s heralded a new era for the CIS outreach program. The new CIS contracts included funds to support one health educator, starting in October 1990. The health educator, a key point person in each CIS region for the implementation of OCC education initiatives, was envisioned as the first step in solidifying the role of the CIS as field offices for OCC.

Defining the Outreach Role

Through the experience of the PIP program, OCC recognized the vital role that the CIS played, working through the media and intermediaries, in stimulating interest in NCI programs at the local level and in providing the necessary support to ensure implementation of program activity.

Using the CIS in this intermediary-based role constitutes a model that differs from the traditional principles of community participation. In the traditional model, to achieve change in a community (such as to increase knowledge about a type of cancer), the target population must be involved in identifying the problem and in setting priorities and goals (18). Effective community participation

Table 2. Evolution of CIS outreach program

Year	Initiative	Purpose	Outcome	Barriers/ recommendations
1975	First CIS contracts: CIS required to plan and conduct public and professional education in cooperation with other agencies and organizations concerned with cancer. Emphasis on collaboration with local community groups, especially ACS, schools, and media.	Increase the reach and impact of local programs, assist in establishing programs to reach professional and public audiences, establish a channel of communications to relay local needs to the cancer center.	CIS increasingly recognized as more than a telephone system; role as the generator of education programs tailored for target audiences growing.	Establishment of telephone service given major emphasis during this "start-up" phase.
1976	Outreach assigned as an NCI comprehensive cancer center characteristic; each center required to determine the needs of the community and designate target groups and program priorities.	Communicate results of research and coordinate cancer service and educational program planning with the development of regional Health Systems Agency plans.	Emphasis on educational programs for professionals, patient/family education programs, rural outreach programs, nurse-to-nurse referral service, medical journal columns.	Diverse set of activities with little cohesion, no feeling of network, and little direction from the national level. Telephone service continues to be major focus of most CIS offices.
1978	Merit review of first 3 years of CIS program.	NCI examines the contribution of the CIS to NCI objectives.	Renewal of contracts with delineation of outreach activities for public education and allied health professionals.	Difficulty of separating CIS outreach from other cancer control activities at the centers; limited plans to identify and reach specific target audiences and allied health professionals with cancer information.
1978	CIS contract renewal.	Revised CIS guidelines include outreach for at-risk target populations. Budgets permitted addition of half-to full-time position for outreach.	Educational programs for health professionals and the public, speakers for community groups. National task forces on African Americans and Hispanics organized. Several offices aim outreach to these target groups.	Multitude of programs, many of merit. Most have little relationship either to one another or to the national program as a whole.
1978	OCC establishes CIS direction based on national priorities and research.	Ten-market follow-up campaign for asbestos workers; conferences, training workshops, and mass media promotion; program in hospitals, for nurses and office-based physicians, to promote breast self-examination.	Increased experience in using intermediary organizations to provide access to target groups; added credibility to NCI programs and messages, furnishing added resources and expertise and program cosponsorship.	Intermediary approach recognizes inability to engage communities using bottom-up strategies; OCC can take advantage of established relationships between intermediary organizations and the community.
1980	Special projects incorporated into CIS work scope; NCI-specified format for approval for outreach projects, including problem definition, target group focus, program goals and objectives, implementation plan, and evaluation criteria.	NCI CIS program directors sought to give more structure and definition to local CIS outreach efforts; greater emphasis placed on outcome evaluation of outreach efforts.	Some projects have lasting effects. CIS becomes more experienced at program planning and more involved with cancer-communications research.	Additional structure strengthens program.
1984	New national 800 number (1-800-4-CANCER) and NCI major initiative on cancer prevention.	To convey the growing body of "good news" about cancer prevention to dispel negative and pessimistic attitudes toward the disease.	Increased recognition and use of the new CIS toll-free number; more focused outreach efforts on cancer prevention and the information needs of special target groups.	

Table 2. Evolution of CIS outreach program—Continued

Year	Initiative	Purpose	Outcome	Barriers/ recommendations
1985– 1987	PIP campaign.	To create a broad public awareness of cancer risk factors and prevention. Utilize CIS network to build local coalitions for cancer-prevention program planning and implementation.	All CIS offices participate, aiding NCI to achieve broad media and health professional coverage. Seven regional planning workshops held to inspire and stimulate development and organization of local programs to identify priorities for future programming. CIS becomes focal point for initiating meetings, organizing and distributing planning documents, and conducting other strategic activities.	Many opportunities for programming identified; most successful programs and coalitions developed where the CIS or another lead organization engaged in active follow-up. PIP workshops serve as a catalyst for many new cancer-prevention activities; collaboration among regional organizations often initiated or strengthened; recommendations led to new OCC publications and activities.
1985	Detroit Program for Black Americans.	Nationwide media campaign with African American celebrities, Joint Health Venture, NCI, and leaders of major African American organizations; promotion of prevention information within local communities.	National program launched in Detroit, included use of Aretha Franklin tapes; local coalition established under staff leadership of CIS of Michigan.	Assess community's unique characteristics, allow enough time for coalition building, design program to fit into other community-based activities, involve gatekeepers in the process, encourage buy-in to program by community leadership, draw in national leadership to help establish concrete identity for collaborative efforts, maintain communication among program participants, have concrete and attainable objectives, conduct ongoing evaluation of program efforts, and use results to plan future activities.
1985	CIS contract renewal.	NCI-DCPC implements drastic budget cuts, eliminating outreach positions from contracts.	CIS outreach efforts restructured or eliminated. Some local offices continue outreach with local support, but overall effort at coordinating outreach from NCI weakened.	Continuity of support for local outreach efforts interrupted, and many continuing efforts terminated.
1987	OCC MAOs: new mechanism by which OCC could issue contracts to applicants for specific outreach developmental projects.	Assist NCI in pretesting or piloting outreach methods and messages. Contracts awarded for the following: 1) to evaluate the effectiveness of the PIP speakers' kit, 2) to find approaches to outreach for African American communities, 3) to develop materials on survivorship for use by intermediaries, 4) to design outreach approaches on breast and cervical screening for low-literacy groups.	See Table 1 for details of MAO-funded projects.	One-year MAO mechanism is not sufficient to plan, implement, and evaluate the effectiveness of major outreach efforts.

Table 2. Evolution of CIS outreach program—Continued

Year	Initiative	Purpose	Outcome	Barriers/ recommendations
1990	CIS contract renewal.	NCI funds awarded to all CIS offices to support one outreach staff position.	OCC and CIS offices clarify role of health educator/ community outreach coordinator. Position designed to focus on program development through intermediaries rather than direct education program. Each CIS office directed to select a target audience on which to focus all outreach. OCC specifies common "theme" for all outreach, e.g., breast-cancer-screening awareness. All local offices required to develop strategies and tactics to accomplish OCC goals and objectives.	Broad range of activities successfully implemented. Evaluation difficult. Core activities and common tactics developed for implementation.
1992	OCC directs outreach efforts to intermediary development.	CIS to serve as a resource to other NCI-funded programs (NBLIC [National Black Leadership Initiative on Cancer], ASSIST, and community cancer programs) and non-NCI-funded programs (e.g., CDC Breast and Cervical Screening program).	CIS outreach coordinator serves as networking catalyst, seeking to foster communication and coordination among various cancer-concerned organizations both regionally and statewide. Effort focused on reaching the "hard-to-reach."	CIS positioned to take proactive approach on intermediary development as new cancer-control issues emerge from OCC. CIS community outreach coordinator role more clearly defined. CIS assists in reducing duplication of efforts among organizations.

requires that the community shape its own direction, develop necessary self-help skills and resources, and have a structure to elicit and/or coordinate the citizen effort (19). An underlying assumption in traditional community participation principles has been that the community must be empowered to control the intervention and must accept ownership of it.

In contrast, the OCC intermediaries model recognizes its inability to engage communities using bottom-up strategies. Indeed, working through intermediary organizations that have a history of community involvement and specific missions to engage the communities prioritized in OCC initiatives, the OCC model attempts to take advantage of already established relationships between the organizations and the community. This approach is also consistent with the national goals and initiatives that have already been established by OCC and are specially designed for the target audiences but which need to be diffused at the community level. This model, unlike community-based strategies that are more labor intensive, is also synergistic with the national media because of the established relationships with national intermediaries and their local counterparts. The OCC intermediaries model more closely resembles change-agent models in which external agents determine the goals and action strategies and then seek to organize coalitions of concerned interests to attack the problem (20).

In the first 6 months following the award of the 1990 CIS contracts, OCC and the CIS offices worked to clarify the structure of the outreach program. First, it became necessary to define the health educator's position more specifically. With only one full-time person committed to outreach in each office, it was clear that the health educators could have little effect if they assumed responsibility for conducting individual outreach programs and activities. Rather, the responsibilities needed to be broader, allowing that person to serve as a catalyst for community activities. Instead of providing programs directly, the health educator was to work with local media and intermediary organizations to bring the NCI program messages and materials to their respective audiences and memberships.

Name Change: Community Outreach Coordinator

The health educator position was subsequently renamed "community outreach coordinator" to reflect this role more accurately. In addition, program initiatives were directed by OCC, based on national priorities. This structure was designed to prevent a repetition of the problems encountered with the CIS "Special Projects," which focused on local needs but did not match NCI priorities. Further, the local outreach program activities were to focus specifically on underserved target audiences as des-

igned by OCC. These target audiences included African Americans, Hispanic Americans, older Americans, and populations with low literacy rates. Thus, even though the CIS activities were to be uniform in the program area addressed (e.g., breast-cancer screening), each CIS office could tailor these messages to reach the most appropriate target audience(s) for its area.

By October 1990, the majority of the community outreach coordinators were hired, and the process for selection of target audiences had begun. Ultimately, 10 offices chose to target African Americans; six, Hispanic Americans; eight, older Americans; and four, populations with low literacy rates. Due to the diverse nature of some service areas, a few offices chose to target more than one audience. For example, the California CIS chose to target both African American and Hispanic audiences, and the Hawaii CIS chose both low-literacy populations and Native Hawaiians.

Working With the New Structure

OCC selected breast-cancer screening as the first national education initiative to be implemented through the new CIS outreach program structure. For planning purposes, each office was provided with a common goal and common objectives for the initiative:

Goal

- To decrease the cancer mortality rate attributable to breast cancer.

Objectives

- To increase the percentage of women ages 40 and over who get an initial screening mammogram and clinical breast examination within the next 2 years from 64% to 85%.
- To increase the percentage of women ages 40 and over who get regular screening mammograms and clinical breast examinations from 31% to 80% by the year 2000.
- To increase the percentage of primary-care physicians who refer asymptomatic female patients ages 40 and over for regular screening mammograms from 37% to 80% by the year 2000.

The offices were then charged with the development of an annual plan to support those program objectives through two broad strategies: 1) keep breast-cancer screening on the media's agenda as a critical preventive health service for women ages 40 and over and 2) develop and disseminate educational materials through organizations serving the target audience.

Initially, no further guidance was provided to the offices. OCC relied solely on the expertise of the offices to identify the most appropriate media and intermediary channels for their respective target audiences. As a result, the quality of the plans varied widely. Although some offices proposed carefully tailored media and intermediary activities, other offices, it was evident, lacked the background and expertise to develop the plan. In addition,

the range of activities was so broad that evaluation of the program was difficult.

Developing Common Tactics

In an effort to build on the expertise that did exist within the network, the CIS offices targeting each audience were asked to identify a few core activities or "common tactics" that they could implement for each audience. The variation in the offices, both in the size of the geographic area served and the resources available to implement specific programs, made this process difficult, but a number of common tactics were developed for implementation. These included the following:

Tactics for African Americans

- Mounting a radio campaign targeting African American-oriented AM/FM stations, including jazz and gospel music stations, with live-announcer script PSAs.
- Developing work site programs targeting employers with a high population of African Americans.
- Facilitating physician mailings to members of the National Medical Association, including breast-cancer screening materials targeting African American women over 40.

Tactics for Hispanic Americans

- Distributing a taped radio PSA from Lupe Ontiveros, targeting Hispanic women, to radio stations with large Hispanic audiences.
- Distributing newspaper clip art/health columns for use in Spanish-language newspapers and Hispanic church bulletins.
- Translating the breast-cancer screening speaker kit into Spanish for use with Hispanic community organizations.

Tactics for Older Americans

- Developing a media kit on breast-cancer screening highlighting the specific issues related to breast cancer and women over 65.
- Conducting a radio talk-show campaign and providing materials for the interviewer and the training materials to prepare local experts to appear on the talk shows.
- Developing newsletter articles and clip art for use by local American Association of Retired Persons (AARP) centers, senior centers, councils on aging, women's clubs, and other community organizations serving women 65 and over.

Tactics for Low-Literacy Populations

- Distributing NCI's "Once a Year for a Lifetime" half-hour video to local television stations including a control/intervention study examining whether local follow-up increases use of programs.
- Disseminating breast-cancer publications designed

specifically for limited-literacy audiences and written at a third- to sixth-grade level to intermediaries who have access to these populations (e.g., public-health clinics, adult education programs) for use in one-on-one counseling sessions.

Intermediary Approach Redefined

In 1992, the focus of the breast-cancer screening initiative shifted to intermediary development. Again, the specific role of the community outreach coordinator needed to be further clarified to identify this role in working with the media and intermediaries more specifically. The role is twofold.

First, the CIS serves as a resource and provides a networking function to both NCI-funded (National Black Leadership Initiative on Cancer, National Hispanic Leadership on Cancer, National Appalachian Leadership on Cancer, cancer centers, American Stop Smoking Intervention Study [ASSIST], etc.) and non-NCI-funded (ACS, health departments) community organizations. CIS can encourage the use of NCI programs and materials and foster communication and coordination among the various organizations, thereby not only reducing the duplication of effort among organizations but also enhancing consistency and focus of messages delivered. For example, partnerships in some communities have developed joint efforts to reach the media with health messages, thus presenting the media with a strong united front rather than several individual and competing messages.

Second, the CIS is positioned to take a proactive approach in intermediary development. This approach involves working with local affiliates of national organizations that have agreed to adopt OCC's education initiatives and identifying new local intermediaries that may be unique to their service area who provide a new entree to the target audience. It also involves assuming a major role in working with the media, including identifying credible spokespersons throughout the service area.

The focus on intermediary development offers the CIS a significant and challenging role in community outreach. It provides the opportunity to reach typically "hard-to-reach" populations through individuals and organizations such populations respect and trust. A community outreach coordinator can give technical assistance to a variety of organizations targeting different audiences, thereby accomplishing much more than even the most competent health educator acting alone.

The challenges of working effectively with intermediary organizations are significant, however. As demonstrated in the MAO church programs in Pennsylvania and Detroit, the process of gaining the interest and trust of intermediary organizations can be difficult and time consuming. Thus, both the local CIS and OCC must be patient in evaluating the outcome of these efforts.

In addition, the capabilities and resources of organizations vary and the CIS must be prepared to adjust to these differences. It must be both flexible and innovative in the implementation of specific program activities.

Finally, organizations will invariably have needs that

neither the CIS nor OCC can meet. It will be critical for both the CIS and OCC to understand that they cannot fill every need and yet still be responsive to their own mission. This will require the development of procedures for helping organizations meet their objectives through the use of materials and resources from other organizations.

Changing Role of the Community Outreach Coordinator

As the outreach component of the CIS program has evolved, the role of the community outreach coordinator has become better defined. The position is clearly not cast in the traditional health-education mold. Although a sound background in health-education theory is helpful, an individual interested in the direct provision of education programs would quickly become frustrated in this role. The position requires a broad range of skills, including the abilities to motivate organizations and individuals, to work with the media, and to negotiate the role of organizations in community programs. Maturity, diplomacy, and patience will be the hallmarks of this position. As the CIS outreach program expands, the community outreach coordinator will also have responsibility for the direction and supervision of outreach staff throughout the region being served.

Relationship With the CIS Phone Service

When the new regional program structure for the CIS was first discussed, consideration was given to separating the phone service and the outreach component into different contracts. The local offices objected, noting that linking the two entities makes a much stronger field arm for OCC.

OCC is playing an integral role in this linkage by considering a comprehensive planning process for education initiatives that utilizes the strengths of both the phone service and the outreach component. For example, a breast-cancer screening initiative could, in the future, incorporate the proactive counseling on mammography (21). A clinical trials education initiative (22) might be expanded to include an outreach component. This more comprehensive approach to the development of education initiatives will expand the reach of OCC's education initiatives exponentially.

FUTURE OPPORTUNITIES

After 15 years of experience, some issues still remain concerning the most effective role of the CIS outreach component. This experience has offered some critical insights, however, and has clarified the questions to be answered.

Structure of the Program

History teaches us that it is most appropriate for OCC to set the education agenda for the outreach program. Therefore, OCC should continue to select the education

initiatives to be implemented based on NCI program initiatives. The program must include a feedback mechanism, however, to ensure that the OCC priorities adequately reflect the needs and concerns of the community. The task force structure that has worked in the past can help to bring the local needs and problems to the table (1).

The level of structure that should be imposed on the development of activities to address the nationally identified initiatives remains an open question. There is a strong argument that specific program activities should be decided at the community level, to ensure that they reflect community needs and to foster community ownership of the program. Under this structure, however, the quality of programs will vary, and duplication of effort across and perhaps even within CIS regions may result. Alternatively, a more directed approach that provides the CIS with specific program interventions (e.g., work site programs) would provide more consistency and more opportunity for measuring impact. Such programs would be developed with CIS participation in the planning process and with room for local adaptation.

Evaluation Schema

Evaluation must be based on a clear understanding of what the OCC program hopes to achieve through its education and media efforts and the specific contributions it expects from the CIS. Appropriate nationwide evaluation is not possible without, at minimum, a common objective, common strategies, and common tactics for implementing the objective and a core set of evaluation criteria that are used uniformly by all CIS offices. Valuable evaluation could be conducted with nationwide dissemination of a specific, well-developed outreach program, using standard materials, procedures, and evaluation tools.

Both formative evaluation and implementation evaluation need to be considered. Evaluation might include targeted local community surveys of cancer knowledge, attitudes and behavior, and awareness of the CIS. Other tools can be used to evaluate the specific contribution of the CIS to overall program strategies. In addition to using surrogate measures, such as documenting the number of calls received by the CIS phone service as a result of specific outreach activities, evaluation activities should include efforts to assess the effectiveness of the CIS in serving community intermediaries. Evaluation tools might include an outreach contact form similar to the CIS Call Record Form that documents the number and type of media and intermediary contacts made by the CIS. User surveys to follow up with intermediaries would also be useful.

In addition to programwide evaluation, office-specific evaluations should be conducted to assess the outreach program of individual CIS offices. Recently, the OCC Plans Board, an advisory body for the OCC programs, considered this issue at length. The board recommended that OCC evaluate CIS outreach activities based on the geographic diversity achieved by the office (Are they reaching their entire service area or only certain portions of it?), the depth of the outreach contacts (Are they sim-

ply distributing booklets, or are they involved in the development of actual program activities?), and the appropriateness of the outreach activities (Are they targeting the right audiences, and are they doing it in an appropriate manner?). It will be critical that the methods of evaluation are developed with local office input through the Evaluation Task Force and are clear to the CIS offices from the outset. In addition, the evaluations must be frequent enough to measure change.

Research Efforts

Many questions remain about the outreach program. OCC should encourage investigator-initiated research to address these issues. One mechanism might include a revitalization of the Cancer Communications System grants that resulted in the work reported in this monograph (21,23-26). Other NCI grant mechanisms might provide broader and more comprehensive evaluations of the program. Specifically, OCC needs to assess the effectiveness of the CIS in helping it achieve the goals of its national programs. Careful attention should be paid to examining the structure of the outreach component to determine the level of structure that should be provided for local program activities. Finally, OCC should encourage an evaluation of the outreach program at the community level, to determine the most appropriate role for the community outreach coordinator and to assess the environment, resources, education, skills, and personal characteristics that make an individual successful in that position.

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The Cancer Information Service Telephone Evaluation and Reporting System (CISTERS): A New Tool for Assessing Quality Assurance

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With more than 500 000 annual telephone inquiries from the public, health professionals, and others, the toll-free telephone-based Cancer Information Service (CIS) has rapidly evolved into a primary contact point and resource for people seeking cancer-related information. As the CIS continues to grow, quality-assurance issues are increasingly important both to maintain a high quality of responses to callers and to ensure the accuracy of information transmitted. The Cancer Information Service Telephone Evaluation and Reporting System (CISTERS), a computer-based interactive interviewing system, is being developed to provide quantitative measures of various aspects of the quality of CIS responses to telephone inquiries. In addition to supplying quantitative feedback to both the National Cancer Institute (NCI) CIS office and the regional CIS offices, CISTERS also allows program managers to identify and provide for staff training needs. CISTERS is a substantial part of NCI's commitment to quality control and assessment of needs within the CIS network and may have significant implications for the growing number of other national telephone-based, health-information helplines. [Monogr Natl Cancer Inst 14:61-65, 1993]

INTRODUCTION

Sponsored by the National Cancer Institute's (NCI's) Office of Cancer Communications (OCC), the Cancer Information Service (CIS) is a nationwide network of 19 regional offices which are designed to provide accurate, up-to-date information on cancer to patients and their families, to health professionals, and to the general public via a toll-free telephone system. The CIS handles more than 500 000 inquiries annually on a variety of cancer-related topics, including early detection, diagnosis, treatment, rehabilitation, and continuing care (*1*). Calls to the CIS are answered by NCI-trained cancer information specialists. These specialists are trained to meet performance standards mandated by CIS program staff at NCI. Emphasis is placed on adherence to CIS operating policies and procedures developed by the NCI/CIS program staff.

This paper describes the development and initial implementation of a quality-assurance program known as the Cancer Information Service Telephone Evaluation and Reporting System (CISTERS). CISTERS evaluators place and tape-record test calls to the CIS network, then document, evaluate, and report their findings. The goal of the

CISTERS program is to obtain a scientifically sound assessment of the level of service to the public and to determine whether improvements are needed. This paper details the objectives of the program and the methods used for collecting and evaluating data.

QUALITY ASSURANCE AND THE CIS: BACKGROUND

In the past, quality-assurance efforts at the CIS have focused on training, continuing education, regular office reports, site visits, a standardized monitoring and supervision infrastructure, and test calls. Since the inception of the CIS, regional offices have been required to conduct local test calls on a regular basis, but there has never been a systematic method to evaluate these calls consistently at the national level. In 1980, a CIS Evaluation Task Force determined that a test-call approach at the national level was an appropriate methodology for evaluating several identified dimensions of quality. Based on that recommendation, efforts at conducting test calls began on a national level at NCI. Test calls were placed to local CIS offices by NCI staff using a standardized format which included "scenarios" or scripts of dialogue for the callers to follow (*2*). Scenarios were developed based on questions callers commonly asked the CIS, such as screening recommendations for breast cancer. These initial test calls involved two NCI staff: one to act as the "caller," the other to listen on another telephone to document and monitor the call. Responses were then evaluated using standard criteria that included accuracy, convenience (e.g., getting through to the office), appropriateness, staff sensitivity, and effectiveness. With the exception of accuracy of information, these criteria were not specifically defined. Thus, differences of opinion sometimes occurred among NCI evaluators concerning the rating of a call. In addition, there were logistic problems arising from telephone availability (need for two phones), time-zone differences at the various offices across the nation, difficulties in documenting lengthy calls, and the increasing ability of offices to identify the NCI callers and thus bias results. Due to these difficulties (as well as others), plans for the national test-call system were never completed.

Other, more sporadic national test-call efforts have included the placement of calls from NCI to assess special

*See "Notes" section following "References."

initiatives or to evaluate responses to a specific and current issue. These included the coordination of test calls in response to an NCI clinical trial initiative on pancreatic cancer in 1988 as well as an assessment of cancer pain control information dissemination in 1991.

OBJECTIVES OF THE CISTERS PROGRAM

In the late 1980s, emphasis was once again placed on the need for a national, comprehensive, systematic quality-assurance program involving test calls. As such, discussions began with the NCI Division of Cancer Prevention and Control's Applied Research Branch on the creation of a scientifically valid test-call system. CISTERS is under development as a joint project between the CIS and the Applied Research Branch as a quality-control system. CISTERS is being designed to do the following: 1) to report on the quality of responses to CIS inquiries, 2) to provide a management tool at the national level, 3) to provide feedback to local CIS offices on various dimensions of quality, 4) to identify training and resource needs, and 5) to assist in the direction of other NCI-OCC-CIS projects.

EVALUATION CRITERIA

Initially, a small number of test-call scenarios were developed by NCI staff with accompanying evaluation criteria. These criteria fall into three natural categories we refer to as "objective measures" (evaluation of the mechanics of calling a CIS office), "completeness measures" (evaluation of technical information provided), and "quality measures" (evaluation of the manner in which the information was conveyed).

Objective measures generally refer to operational aspects of placing test calls—for example, the number of rings in which a call is answered, whether a test caller is placed on the sequencer (i.e., the caller hears a recorded message and is placed on hold), and for how long the caller waits on the sequencer. The proportion of test calls resulting in a busy signal is one key operational measure. These objective measures inform the national CIS office about systemwide performance of basic operations and may indicate resource-allocation problems.

Completeness measures examine the accuracy of technical information one would expect to receive in response to a specific question. For example, the complete information expected by CISTERS for an older woman asking if she should have a mammogram would include the following: 1) asked age of caller, 2) asked if caller was asymptomatic, 3) asked if caller ever had a mammogram, 4) explained that mammography is a screening test that can detect changes in the breast, and 5) explained that NCI recommends that all women over the age of 50 receive an annual mammogram.

Quality measures continue to be specifically defined and refined over the course of the development of the CISTERS program. Initial quality measures consisted of

credibility (appropriate citation of resources), use of technical terms, confirmation of caller's understanding, attitude and professional demeanor, sensitivity, and communication skills (including speed and clarity of speech, organization of call, and use of active-listening skills).

For several reasons, the test calls are recorded. Recording calls allows the test caller to focus on the task at hand: convincing the CIS specialist that this is a "typical" call and moving from question to question as smoothly as possible. It also allows for thoughtful coding of the responses to the questions after the call is completed. The recordings provide an accurate (and irrefutable) record of calls in the event that an office needs to be contacted about any important problems that have occurred. Finally, the recording allows for reliability testing of the coding of the calls.

DEVELOPING SCENARIOS FOR THE TEST-CALL SYSTEM

Topics for test calls are selected from CIS-identified "typical" inquiries, previously used test calls in which quality-control problems surfaced, and suggestions from CIS and NCI staff. The following topic areas are also incorporated: NCI national outreach initiatives, application of new or established written resources, recent medical and scientific breakthroughs, written NCI-CIS program policies and procedures, and the ways in which offices provide local medical or social support referrals. For example, test calls include scenarios ranging from simple inquiries such as whether annual screening mammography is appropriate for women over the age of 50 to more complicated inquiries such as the treatment options for advanced pancreatic cancer. Within these more complex scenarios are additional collateral issues such as staging, clinical trials, and descriptions of different diagnostic tests, any of which may require explanation.

Once a test-call topic is selected, a test-call scenario is developed using a standardized format that consists of the caller's background, sample questions from callers followed by an appropriate (and expected) CIS response, and identification of essential elements of NCI policies and procedures. NCI and CIS written material, such as informational publications, Physician Data Query (PDQ) statements, and NCI "Fact Sheets," are often used in the development of test-call scenarios for three reasons: these materials are primary resources provided and required by NCI, they are available to all CIS information specialists, and they are routinely used for CIS training and continuing education (3).

TEST-CALL METHODOLOGY: RELIABILITY AND VALIDITY

After scenarios are developed and edited by NCI-CIS program staff, the next step is to test the reliability of the coding to ensure CIS offices that the reports generated by

CISTERS reflect consistent, accurate measurement of the completeness and quality dimensions. Reliability testing includes training test callers for conversational fluency using each new scenario, followed by testing and recording about eight calls per scenario. Next, the recorded test calls are evaluated (or coded) by a panel of raters consisting mainly of staff from local CIS offices. Input from these raters is invaluable in developing an accurate and scientifically valid tool for assessing quality. Finally, reliability statistics for each of the items are calculated. The sample size, or number of calls made for each scenario, and the number of raters reflect statistical power calculations developed by NCI staff (C. Brown: personal communication, 1992). These calculations are based on hypotheses of attaining a high degree of agreement among multiple raters during the reliability test panels.

After the reliability statistics are calculated for each of the items, those items which fare poorly are then scrutinized by the rating panel. Items deemed critical to the flow of the scenario might be rewritten and retested later in a revised scenario.

Measures of quality, such as correct information, length of time on hold, number of rings before the call is answered, and whether the call is answered with the greeting "Cancer Information Service," are absolute and easily quantified, resulting in 100% agreement among all raters (see Table 1). Although agreement among raters tends to be quite high for the evaluation criteria of completeness, partial information delivered by the information specialists can provoke different ratings by panelists. Generally, this discrepancy is addressed by abbreviating the amount of information expected for a CISTERS test call. Disagreement among raters is more likely when they attempt to measure "subjective" dimensions of quality such as the degree to which the CIS information specialist exhibited credibility, organization of information, and sensitivity to the caller (Table 2). Even with apparently clear definitions, raters often have varying perceptions of these qualitative dimensions as well as the degree to which they are satisfactorily met by the information specialist (4,5).

PRELIMINARY RESULTS AND IMPLICATIONS

The preliminary reliability tests of CISTERS demonstrated it to be a reliable, valid, and feasible measurement tool. At the same time, these preliminary tests revealed several technical problems which were subsequently resolved. For example, based on the initial reliability tests, additional test-call interviewers were recruited, improved identification information was provided to interviewers (local ZIP codes, cities, and health-care institutions in the calling areas), and increased attention was given to the completion of the computerized operation of CISTERS to provide easier data entry and improved output for the reliability testing. In addition, reliability testing was criti-

Table 1. Quality control "flags"

Item	Definition	Coding categories
Major problem	Significant problem requiring management intervention (e.g., inaccurate information given)	Yes/no
Excessive time on hold	> 5 minutes	Yes/no
Excessive number of times on hold	> 5 times	Yes/no
No information offered	Only written materials offered	Yes/no
Personal judgments given	Personal opinion given as fact	Yes/no

cal in defining what constitutes a "good" call. This process enabled CIS program staff to redesign scenario criteria that were more representative of a typical call, while at the same time specifying and clarifying definitions of quality to minimize individual differences of interpretation.

Early results showed ambiguity among reliability panelists in areas such as "misinformation given." For example, in some cases the information given was accurate, but it was not relevant to the caller's specific question; in other cases the information given was far more extensive than required by the scenario. By including and encouraging the active participation of CIS network and NCI staff in the reliability process, the system has evolved into a comprehensive and "user-friendly" tool for measuring overall accuracy and consistency of cancer-related information.

IMPLEMENTATION OF CISTERS

After the scenarios have gone through a successful reliability test, they are eligible for inclusion in the CISTERS implementation phase. In this phase, a larger number of callers will be employed to call CIS offices with different scenarios. Initially, each CIS office is scheduled to receive two calls per week. Implementation of CISTERS has been initiated twice, but staffing problems have prevented NCI from placing CISTERS on a continued operating basis. As soon as sufficient operational data become available, analyses to determine the appropriate number of calls will be undertaken. Eventually, CISTERS will operate on a quality-control sampling system in which offices that perform very well will have call frequency reduced over time, and offices that perform poorly will have call frequency increased until sufficient data can be collected to confirm the nature of any problems and suggest solutions. Then, call frequency will remain at an elevated level until the office has improved its quality.

Table 2. Subjective dimensions of quality

Item	Definition	Coding categories
Cites resources	Complete identification of resource materials used (NCI publication, PDQ database, other medical text) is given.	Completely cited Incompletely cited Did not cite
Appropriateness of resource	Resources are approved by NCI, current, and appropriate to caller's need.	Appropriate Inappropriate
Use of technical terms	Medical terms and phrases are explained and defined; frequency of explanation.	Complete Partially complete Inadequate
Checked caller's understanding	Ability to evaluate caller's level of comprehending the information and concepts that are shared.	Checked well Did not check well Did not check
Attitude	Information specialist is pleasant, patient, courteous.	Polite Inconsistent Negative
Credibility	Ability to sound believable, competent. Specialist avoids casual remarks and focuses information on the questions asked.	Credible Somewhat credible Not credible
Sensitivity	Specialist displays warmth and empathy and establishes good rapport with caller.	Adequate/poor
Communication mechanics	Information is clear, concise, and delivered at an appropriate pace.	Nonproblematic/problematic
Organization	Specialist asks appropriate questions; information is logical, coherent, and presented in a systematic manner. Information is well thought out and properly integrated in the conversation.	Logical Somewhat confusing Confusing
Active listening skills	Specialist is sensitive, responsive, and brief. Specialist did not interrupt or monopolize conversation. Specialist paraphrases and summarizes where appropriate; allows caller time to reflect on information.	Receptive Somewhat receptive Not receptive
Personal and value judgments	Specialist avoids personal judgments (i.e., giving personal medical advice or personal recommendations). Specialist avoids value judgments ("You should have done . . ."). Specialist avoids discussing previous calls.	Yes/no

DISCUSSION

CISTERS is being designed to augment existing quality-assurance efforts that include continuing education, training, regular office reports, site visits, a standardized monitoring and supervision infrastructure guided by approved policies and procedures, and the network-wide availability of state-of-the-art cancer-treatment information through the PDQ system. Thus, although CISTERS is designed to be an important component of overall quality assurance, it cannot (and is not designed to) replace internal quality-control efforts (such as in-house monitoring of calls) conducted by supervisors at local CIS offices. CISTERS will be useful to each office in augmenting internal test calls as well as assisting in identifying program needs and providing an overall quality measure. It is limited, however, by a lack of specificity—too few calls per office are placed to provide evaluations of individual network staff. We anticipate 100 to 150 calls per office per year in the initial implementation phase.

Ideally, CISTERS will provide feedback to regional offices in at least two ways: by mailing typed transcripts of test-call tapes to the CIS project directors in each regional office and by providing quarterly evaluation summaries. General report summaries generated by CISTERS will afford NCI-CIS program staff the opportunity to offer reinforcement and encouragement in the demonstration of appropriate skills and the opportunity to effect change in areas that require improvement.

To avoid the possibility that regional office staff will rate test-call tapes differently than CISTERS program staff do, reliability testing involving CIS network staff will be done on a regular basis to evaluate the performance of each scenario conducted in the test-call setting. The authors found it important to include CIS staff members representing diverse areas of expertise in this reliability process to share ideas, opinions, and information.

In summary, the American public is increasingly likely to rely on telephone-based health-information resources. In response to this phenomenon, telephone-based health-information services are expanding with respect to cancer,

acquired immunodeficiency syndrome (AIDS), and other conditions (6). By sharing a vision of continual quality-control monitoring to improve the service of the CIS network, CISTERS has the potential to become a model program that can be adapted for use with other health-oriented information helplines, contributing to a better-informed public empowered to actively participate in the health-care process.

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The Cancer Information Service as a Laboratory for Research: The First 15 Years

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Over the past 15 years, the Cancer Information Service (CIS) of the National Cancer Institute has generated a substantial body of research. In the present report, this research is reviewed as it pertains to five key questions: 1) Who uses the CIS? 2) What are the topics of inquiry? 3) How do callers learn of the CIS? 4) Do CIS campaigns and unplanned events affect CIS call volume? 5) Can the CIS influence behavior? Major conclusions from this review can be summarized as follows: 1) The vast majority of callers to the CIS are female, White/Anglo, and of middle-class background. 2) Most calls relate directly or indirectly to cancer-treatment issues. 3) A variety of media and sources are reported by CIS callers, with television ranking high across most studies. 4) CIS call volume can be substantially influenced by promotion campaigns and unplanned events. 5) The available evidence suggests that the CIS can influence behavior, especially information-seeking behavior. Recommendations for future research are discussed in light of the results of this review. [Monogr Natl Cancer Inst 14:67-79, 1993]

INTRODUCTION

Over the past 15 years, the Cancer Information Service (CIS) of the National Cancer Institute (NCI) has generated a substantial amount of research. The vast majority of this research has been descriptive, relying to a great extent on analyses of data obtained from the CIS Call Record Forms (CRFs). The CRFs provide an unusually rich source of data about the CIS and can be analyzed at relatively low cost. As noted elsewhere in this monograph (1), the CRF protocol was implemented in 1983. This protocol requires that CIS information specialists complete a standardized form for each call. To complete the form, specialists ask callers a short list of questions (e.g., how the caller found out about the CIS and the age, race/ethnicity, and education level of the caller). Other questions on the form are answered after completing the call (e.g., nature of the inquiry, suggestions provided by the information specialist). These forms are routinely coded by the CIS network and computer-processed for analysis and program monitoring by the Office of Cancer Communications at NCI. To date, over 3 million CFRs have been completed by the CIS.

Access to the CRFs (and the implied support of the Office of Cancer Communications in providing such ac-

cess) has allowed researchers to examine several key policy and programmatic issues facing the CIS. Prominent among these issues are the following:

1. Who uses the CIS?
2. What are the topics of inquiry?
3. How do callers learn of the CIS?
4. Do CIS campaigns and unplanned events affect CIS call volume?
5. Can the CIS influence behavior?

In this paper, each of these five questions are examined relative to the existing body of CIS research. Recommendations for future research are also discussed in light of the results obtained from this review.

1. WHO USES THE CIS?

The CIS represents a unique social experiment: as one of the first federally funded health-related telephone information systems in the nation, the CIS's mandate is to provide services to a broad spectrum of the population. Thus, the ability of the CIS to provide this service is not only a key policy issue for the CIS but also a matter of general interest to communications researchers. What kinds of people will use a toll-free telephone information service dedicated to a major public-health problem in this country? Will the CIS attract socioeconomically disadvantaged populations and racial/ethnic minorities? Because of the scope and history of the CIS (i.e., continuous funding since 1976, a network of regional offices coordinated and supervised at the national level, toll-free telephone number), researchers who have examined these questions with respect to the CIS have contributed to a broader understanding of telephone information systems in general.

As shown in Table 1, numerous studies have been conducted to profile or characterize the users of the CIS. These descriptive profiles of a "typical" CIS caller are highly consistent across studies and time and indicate that the vast majority of CIS callers are female, White/Anglo, with at least a high-school education. Studies have shown repeatedly that low-income, minority populations underutilize the CIS, despite the fact that they are often at higher risk for certain cancers.

As noted elsewhere in this monograph (1), the CIS continues to be underutilized by low-income populations and racial/ethnic minorities. Recently, a community out-

*See "Notes" section following "References."

Table 1. Examples of studies characterizing the users of the CIS

Authors	Methodology	Selected findings
Ward et al. (4)	Examined national CIS CRF data, 1983–1987.	<ol style="list-style-type: none"> 1. White = 86% of calls. 2. Female = 70%. 3. High-school graduate or above = 89%. 4. General public = 50%. 5. Cancer patients = 11%. 6. Friends/relatives of cancer patients = 22%. 7. Symptomatic callers = 8%. 8. Since implementation of the Publications Ordering Service, calls from general public have dropped from 51% (1985) to 33% (1986) and calls from patients and friends/relatives of patients have increased from 29% to 42%.
Anderson et al. (5)	Examined CIS CRF data, 1983–1989. Excluded calls routed to Publications Ordering Service, which became available in 1985.	Majority of callers were White (88% of calls), female (71%), with at least a high-school education (88%). Calls from general public = 39%; calls from cancer patients and friends/relatives of cancer patients = 41%.
Manfredi et al. (6)	Compared cancer patients who called the Illinois CIS (n = 257) with other cancer patients in Illinois (n = 262).	<ol style="list-style-type: none"> 1. CIS cancer patients more seriously ill. 2. CIS cancer patients more stressed by their illness. 3. CIS callers more likely to be female, younger, with higher education. 4. CIS callers more likely to be in treatment. 5. CIS callers more likely to talk to others about their cancer and to visit more physicians and hospitals.
Duffy (7)	Examined CIS CRF data, 1988–1989. Excluded calls to the Publications Ordering Service.	Between 1988 and 1989, there was an increase in the percentage of calls from cancer patients or friends of cancer patients (45% versus 52%) and a corresponding decrease in calls from the general public (32% versus 28%). Percentage of callers with at least some college education has increased (55% versus 61%). Percentage of callers who are White has remained constant (89%).
Stein (8)	Examined national CIS CRF data, 1983–1984.	Majority of callers were female (71%), with at least some college (54%). Whites accounted for 89% of calls; African Americans, 7%; Hispanics, 3%.
Reiches and Brant (9)	Examined CRF data from the Ohio CIS, 1979–1980.	<p>Majority of callers were women (78%).</p> <p>General public = 32%.</p> <p>Cancer patients = 13%.</p> <p>Friends/relatives of cancer patients = 33%.</p>
Mettlin et al. (10)	Examined CRF data from the CIS at Roswell Park Memorial Institute, 1977–1978.	<p>Majority of callers were women (75%).</p> <p>General public = 42%.</p> <p>Cancer patients = 10%.</p> <p>Friends/relatives of cancer patients = 19%.</p> <p>People with symptoms = 13%.</p>
Kean et al. (11)	Examined CIS CRF data from the Texas CIS, 1980.	Rural populations underutilized the CIS. Census data indicate that 78% of population lived in Standard Metropolitan Statistical Areas, compared with 93% of CIS callers.
Azzara et al. (12)	CIS CRF data were aggregated by counties, cities, or towns and combined with 1980 census data to allow calculations of CIS call rates. Geographic areas included Massachusetts, New Hampshire, Maine, and Vermont.	<ol style="list-style-type: none"> 1. Most highly urbanized counties were overrepresented among CIS callers. No difference in call rates among moderately urbanized and low-urbanized counties. 2. Lower CIS call rates among older, industrialized cities. Cities with highest call rates had major news media or active cancer centers. 3. Income and education levels of cities/towns positively correlated with CIS call rates; percentage of Hispanics negatively correlated with call rates.

Table 1. Examples of studies characterizing the users of the CIS—Continued

Authors	Methodology	Selected findings
Parker et al. (13)	Examined local CRF data from the CIS at Howard University, 1978–1981.	Females = 72% of total calls; Whites = 71%; African Americans = 29%; calls from general public = 81%.
Freimuth et al. (14)	Examined national CIS CRF data, 1983–1986.	<ol style="list-style-type: none"> 1. 71% of CIS callers = female. 2. 53% of CIS callers = at least some college. 3. 10% of CIS callers = African American or Hispanic. 4. 11% of CIS callers = cancer patients. 5. 22% of CIS callers = friends/relatives of cancer patients. 6. 47% of CIS callers = general public. 7. 8% = symptomatic callers.
Meissner et al. (15)	Examined national CIS CRF data, 1983–1987.	<ol style="list-style-type: none"> 1. Females = 70%. 2. White = 89%; African American = 6%; Hispanic = 3%. 3. High-school education or above = 88%.

reach program designed to increase the reach to special populations (1) has been added to the CIS. In addition, both Ward et al. (2) and Arkin et al. (3) cite examples of successful CIS promotional campaigns that targeted minority populations. These examples, however, are few and far between and, thus, serve to highlight what is possible, rather than what is routine, within the CIS network.

Most studies report that 40%–50% of the calls are from cancer patients or friends/relatives of cancer patients and fewer calls are from the general public. The dates of the studies in question are significant, however. The earlier studies (prior to 1985) often report a higher percentage of calls from the general public than do the more recent studies. Those earlier studies must be interpreted within their historical context because the CIS Publications Ordering Service (POS) was not yet in operation. Since 1985, the POS has taken calls (largely from the general public) that involve straightforward requests for CIS print material, resulting in a lower percentage of calls triaged to the regional CIS network from the general public (4,5). It would also appear that a significant number of cancer patients who call the CIS are among the sickest of the sick (6). Thus, not only does the CIS provide services to a substantial number of cancer patients nationwide, but also it tends to serve patients who are more ill and more stressed by their illness than cancer patients who do not call the CIS. This finding underscores the critical role played by the CIS in responding to those in greatest need and highlights the tremendously difficult challenges faced by CIS information specialists on a routine, day-to-day basis.

2. WHAT ARE THE TOPICS OF INQUIRY?

A second category of studies has examined the nature of the inquiries to the CIS (i.e., the type of information being

requested by CIS callers). The CIS is mandated to provide information to the general public, cancer patients, friends and relatives of cancer patients, and physicians and other health professionals. Each of these target groups has different information needs, ranging from primary prevention to tertiary prevention and continuing care. What has the research literature shown with respect to the distribution of information requests received by the CIS? As shown in Table 2, the majority of calls to the CIS have involved questions about cancer symptoms, diagnosis, and/or treatment. A relatively low percentage of calls has involved topics related to cancer prevention, and an even smaller percentage of calls has been concerned with cancer screening.

It is important to note in this regard that the nature of the information requests to the CIS are highly sensitive to unplanned events, as well as to efforts of the CIS to promote a specific type of request (e.g., a 2-week CIS mass-media campaign to promote use of CIS smoking-cessation materials). Duffy (7), for example, reports that requests for information about cancer prevention dropped from 17% to 7% between 1988–1989. This reduction does not imply that questions about cancer prevention are of less concern to the public, because other factors were operating to influence the distribution of these requests, including specific NCI promotional campaigns that targeted cancer patients and clinical trials research. The main point here, of course, is that the nature of the information requests (at any given point in time) must be interpreted within the context of competing events and ongoing CIS promotional activity. Nonetheless, even with this important caveat, we can still observe across studies and time one consistent finding: the vast majority of calls relate in some way to cancer treatment, including second opinions and medical referrals—a situation that is clearly in line with the overall mandate of the CIS. Whether information requests related to primary and secondary prevention are at appropriate levels is another matter.

Table 2. Examples of studies characterizing the information requests of CIS callers

Authors	Methodology	Selected findings
Ward et al. (4)	Examined national CIS CRF data, 1984–1987.	Recent changes in caller type (higher percentage of cancer patients calling the CIS) resulting from activation of the POS (1985) has altered the distribution of inquiries to the CIS. 1. Questions about cancer site: 1984 = 11.2%; 1987 = 18.0%. 2. Treatment-related questions: 1984 = 10.2%; 1987 = 18.1%. 3. Clinical trials: 1984 = 2.9%; 1987 = 4.1%.
Anderson et al. (5)	Examined CIS CRF data, 1983–1989. Excluded from analysis are calls routed to the POS, which became available in 1985.	1. Majority of calls were concerned with cancer site, symptoms, and/or treatment information (30%) and with publications requests (22%). 2. Smoking-cessation inquiries = 14%. 3. Other prevention questions = 10%.
Manfredi et al. (6)	Compared cancer patients who called the Illinois CIS (n = 257) with other cancer patients in Illinois (n = 262).	Most frequent topics of inquiry by CIS cancer patients: 1. Cancer, explanatory = 46%. 2. Treatment, explanatory = 23%. 3. Experimental treatment = 23%. 4. Treatment options = 21%. 5. Referrals = 16%. 6. Coping = 12%.
Duffy (7)	Examined CIS CRF data, 1988–1989. Excluded calls to the POS.	1. Percentage of callers requesting information about cancer site, cancer treatment, and clinical trials increased from 34% to 48%. 2. Percentage of callers requesting information about cancer prevention (excluding smoking cessation) dropped from 17% to 7%.
Reiches and Brant (9)	Examined CIS CRF data from the Ohio CIS, 1979–1980.	Inquiries about cancer treatment = 20% of all calls; general cancer information = 14%; cancer symptoms = 11%; cancer causes = 8%. Only 7% of calls concerned cancer diagnosis/screening.
Freimuth et al. (14)	Examined national CIS CRF data, 1983–1986.	Nationwide, most frequent information requests: cancer risk factors (22%); general cancer information (21%); cancer treatment (17%); cancer prevention (13%). Less than 2% about cancer screening.
Meissner et al. (15)	Examined national CIS CRF data, 1983–1987.	Most frequent topics of inquiry: <u>Significant others:</u> Site information = 26%. Treatment = 13%. Referral/second opinion = 12%. Counseling = 11%. Clinical trials = 10%. <u>Patients:</u> Site information = 25%. Treatment = 13%. Referral/second opinion = 13%. Publications = 9%. Chemotherapy = 9%. <u>General public:</u> Publications = 52%. Smoking = 38%. Primary prevention = 28%. Secondary prevention = 10%. General cancer = 6%.
Stein et al. (16)	Examined national CIS CRF data, 1983–1984.	Inquiries about cancer risk factors = 23%; physician referrals = 24%; treatment and rehabilitation = 19%. Primary prevention and screening accounted for only 11% of all calls.

3. HOW DO CALLERS LEARN OF THE CIS?

A third category of research has examined the way in which callers learn about the CIS. The Office of Cancer Communications has, over the past 15 years, promoted the toll-free telephone number using a variety of media, including television, radio, and print. Local CIS promotions have, likewise, used a variety of media. All are viable policy and programmatic options for the CIS. For this reason, it is essential to understand how people find out about the CIS and what methods seem to be most effective in reaching particular target audiences. As shown in Table 3, television public service announcements (PSAs) rank relatively high across studies. In addition, the studies indicate that television and radio are relatively more effective in reaching low-income, minority populations and that print media is relatively more effective in reaching middle-class, White/Anglo, and Asian/Pacific Islander populations. Although radio is cited as a source of information about the CIS, radio campaigns that specifically target minority populations have not been studied extensively within the CIS. Yet, radio holds great promise in reaching such populations (13,17-23). A similar observation can be made with respect to low-literacy and culturally appropriate print material. The development and distribution of such material has not, until very recently, been a major focus of the CIS, but current efforts by the CIS appear to be headed in this direction (24).

4. DO CIS CAMPAIGNS AND UNPLANNED EVENTS AFFECT CIS CALL VOLUME?

Another line of research has assessed the effects of a particular CIS campaign or unplanned event on CIS call volume. Examples of such research are presented in Table 4. These studies clearly show that CIS promotional campaigns can substantially increase call volume. Evidence for this conclusion can be found in campaigns focusing on smoking cessation, asbestos knowledge and awareness, general cancer information, diet and nutrition, and clinical trials. Of special note is the study by Brown and Potosky (26), in which the investigators examined the impact of President Reagan's colon cancer episode on national CIS call volume and Medicare utilization rates for proctoscopy and stage of diagnosis. The investigators report that President Reagan's highly publicized colon cancer episode had a substantial impact on CIS call volume and was probably linked to increased utilization of proctoscopy. Also intriguing was that the investigators found a significant increase in early detection of colon cancer during this period (1985). This study provides unique evidence of the link between CIS call volume and other population-based changes of substantial significance to cancer-prevention and -control efforts in this country. Apparently, under certain circumstances, CIS call volume may indeed be a good marker of the concerns of the population at large and, thus, could serve as an early warning sign for population-based behavior change (e.g.,

an increased demand for certain medical services such as cancer-screening tests)—precisely because of the theoretical linkage between information-seeking behavior and subsequent behavior change.

Another noteworthy study is that of Cummings et al. (27,28). These investigators provide a textbook example of the impact (i.e., a 10-fold increase in call volume) of a well-conceived and -targeted CIS campaign and the potential cost-effectiveness of paid advertising as a strategy for increasing call volume and promoting population-based behavior change. Similar findings are also reported by Pierce et al. (29) involving three antismoking PSA campaigns.

Also instructive are the results of Arkin et al. (3). Included in their analysis is an examination of the impact of several CIS mass-media campaigns on call volume, including the asbestos awareness campaign (1979), the "Good News" campaign (1984-1985), the Minority Cancer Awareness Week campaign (1985), and the Prostate Cancer Awareness Week campaign (1989-1990). Other events not planned by the CIS are also cited as having a significant impact on call volume; these include articles in magazines and newspapers. Similar results are reported by Freimuth et al. (14) regarding the 1983 U.S. Surgeon General's Antismoking Campaign, the 1985 Aretha Franklin Cancer Prevention Awareness Campaign, and the 1984-1985 Kellogg-NCI collaboration.

Finally, it should be noted that only three studies that tested specific radio campaigns targeting underserved populations (African Americans, Hispanics, rural populations) were found. Strongest support for the use of radio was found for African Americans and rural populations (11,13).

5. CAN THE CIS INFLUENCE BEHAVIOR?

At one level, we have already answered this question in the affirmative. Calling the CIS (i.e., information seeking) is a behavior in its own right that should not be taken lightly; it often represents an intermediate phase or precursor to health behavior change. Although less is known about the impact of the CIS on caller health behavior, virtually all relevant studies support the hypothesis that the CIS can influence health behavior.

In 1984-1985, the CIS network conducted a follow-up mail survey of a random sample of CIS callers who were previously mailed print material ($n = 7530$). Included in this survey was a question asking callers if they had taken a positive health action following their recent call to the CIS (2-4 weeks earlier). More than 90% of the respondents answered in the affirmative. Among the behaviors cited most frequently were the following: 1) read CIS print materials (83%), 2) shared information with others (58%), 3) visited a doctor or made an appointment (24%), 4) sought more information (19%), 5) changed eating habits (16%), 6) attempted to reduce or stop smoking (12%), and 7) learned or practiced self-detection technique (10%). Callers were then asked the extent to which the CIS influenced these recent behaviors. Over 90% re-

Table 3. Examples of studies examining how CIS callers learned of the CIS

Authors	Methodology	Selected findings
Ward et al. (2)	Examined CIS CRF data, 1983–1990, by racial/ethnic group.	<ol style="list-style-type: none"> 1. Television ranked highest across all racial/ethnic groups except Asian/Pacific Islanders. 2. Publications ranked first among Asian/Pacific Islanders. 3. Television ranked especially high for African Americans, Hispanics, and Native Americans (45% or higher). For Whites = 35%. 4. Radio ranked highest among African Americans (10%).
Arkin et al. (3)	Examined CIS CRF data, 1983–1991.	Between 1983 and 1991, 1 731 817 calls received by the CIS. Of these, at least 778 905 (45%) resulted from media promotion. Of those calls resulting from media promotion, the greatest number linked to television (65%), followed by newspapers (14%), magazines and newsletters (14%), and radio (7%).
Stein (8)	Examined national CIS CRF data, 1983–1984.	Television = 35%; print media = 20%; telephone book/directory assistance = 14%; health professional/agency = 11%; significant other = 7%.
Reiches and Brant (9)	Examined local CRF data from the Ohio CIS, 1979–1980.	Newspaper = 20%; television = 11%; American Cancer Society = 22%.
Mettlin et al. (10)	Examined local CRF data from the CIS at Roswell Park Memorial Institute, 1977–1978.	<p>Calls to Roswell Park = 18%.</p> <p>Television = 15%.</p> <p>Telephone directories = 12%.</p> <p>Newspapers = 11%.</p>
Parker et al. (13)	Examined local CRF data from the CIS at Howard University, 1978–1981.	<ol style="list-style-type: none"> 1. Most frequent sources of information about CIS were: <ul style="list-style-type: none"> Television = 23%. Telephone book = 21%. Brochures = 13%. Health professionals/American Cancer Society = 13%. Newspapers/magazines = 6%. Radio = 6%. 2. African Americans responded better than Whites to television (32% versus 19%) and radio (11% versus 5%). Whites more likely to cite print material, including telephone book (24% versus 14%) and brochures (14% versus 9%), and referrals from health professionals and the American Cancer Society (14% versus 9%).
Freimuth et al. (14)	Examined national CIS CRF data, 1983–1986.	Nationwide, 40% of callers identified television. Telephone book/operator = 10%; medical/other referrals = 10%; friends/relatives/co-workers = 8%; all print combined = 15%.
Meissner et al. (15)	Examined national CIS CRF data, 1983–1987.	<p>Most frequent sources of information about the CIS:</p> <p>Significant others:</p> <ul style="list-style-type: none"> Health professionals/agencies = 28%. Print material = 23%. Directory assistance/telephone book = 22%. Friends/relatives = 15%. <p>Patients:</p> <ul style="list-style-type: none"> Print materials = 30%. Health professionals/agencies = 23%. <p>General public:</p> <ul style="list-style-type: none"> Television = 58%. Print material = 15%. Radio = 11%.

Table 3. Examples of studies examining how CIS callers learned of the CIS—Continued

Authors	Methodology	Selected findings
Anderson et al. (25)	Examined 30% subsample of national CIS CRFs, 1983–1987.	<ol style="list-style-type: none"> 1. Television ranked first (males = 72%, females = 61%). 2. Television cited more often among less educated (e.g., <high school = 77%; college graduate = 55%) and more often among African Americans (75%) and Hispanics (79%) than Whites (65%). 3. Publications cited more often among highly educated (e.g., <high school = 5%; college graduate = 19%) and more often among Whites (15%) than African Americans (5%) and Hispanics (5%). 4. Radio cited more often among highly educated (e.g., <high school = 4%; college graduate = 18%).

sponded that the CIS was very (58%) or somewhat (34%) important. Only 3% said the CIS was not important at all (4,14).

In a study conducted by Altman (36), CIS callers who had cancer-related symptoms at the time of their calls, but who were not yet diagnosed, were examined using data obtained from a follow-up survey of 512 CIS callers. Altman found that 75% of the CIS callers who had not made contact with a health professional prior to calling the CIS did so after calling the CIS and that of these callers, only 50% indicated that they definitely would have made contact with a health professional on their own initiative (i.e., without calling the CIS). Altman's study was the first to document the potential value of the CIS in responding to the needs of symptomatic callers nationwide. Other investigations at the regional level have uncovered similar results (e.g., 10,31).

The work of Altman has recently been updated and extended by Manfredi et al. (6) in this monograph. These investigators examined two samples of cancer patients: 1) those who called the Illinois CIS from October 1988 through October 1989 and 2) those who did not call the CIS but were diagnosed and treated at Illinois hospitals. As Altman did, these investigators found that a high percentage (51%) of cancer patients shared the information they obtained from the CIS with their physicians. Nearly 20% of the cancer patients who called the CIS reported that their physicians either requested more information or consulted with another physician about the information provided by the CIS. Approximately 40% of CIS cancer patients said information provided by the CIS helped in making decisions about treatment or care, 12% indicated that CIS information helped them to find a new physician or seek a second opinion, and 10% reported that CIS information helped them decide for or against a particular treatment. These findings suggest that information conveyed to cancer patients by the CIS may indeed influence clinical decisions (37).

Cummings et al. (35) conducted a follow-up survey of CIS callers who responded to a television promotion of the "Diet, Nutrition and Cancer Prevention" booklet.

The promotion was part of the local news broadcast within the nation's largest television market (i.e., New York City, Long Island, southern New York state, northern New Jersey, and Connecticut). A total of 1842 callers to the Roswell Park Memorial Institute CIS were randomly sampled, of which 62% returned their mail questionnaires at 7–9 months' follow-up ($n = 1016$). Over 70% of those surveyed indicated that they had made changes in their eating and/or food-preparation practices after receiving the booklet. Reported changes in dietary practices were consistent with recommendations contained in the booklet, including eating less red meat or pork and/or eating more chicken or fish (56%), eating more whole-grain breads and cereals (47%) or vegetables (43%), barbecuing less often (32%), frying foods less often (63%), trimming fat more often (54%), and baking more often (39%). As noted by the investigators, these results must be interpreted with appropriate caution because of the self-selected nature of the sample (i.e., subjects were already motivated to call the CIS about dietary information). CIS callers are by definition self-selected, however. Assuming that the self-report data are essentially valid, this study seems to indicate that CIS print material may indeed serve as an effective cue to action among those already motivated or contemplating behavior change.

Elsewhere in this monograph, three additional studies are reported which examined the behavioral impact of the CIS on caller behavior (28,38,39). These three studies were funded by NCI as part of the Cancer Communications Systems Research program initiative. As a group, these studies are of special interest because all are prospective intervention research studies. Marcus et al. (38) tested a proactive screening mammography promotional protocol within two CIS regional offices and found that the protocol improved screening mammography at 12 months' follow-up. Cummings et al. (27,28) conducted a study involving telephone follow-up of all smokers who called the local CIS in response to a media campaign conducted by the investigators. The overall self-reported quit rate was 18% at 6 months' follow-up, which compares favorably with other self-help smoking-cessation interventions.

Table 4. Examples of studies assessing the impact of CIS promotion campaigns and/or unplanned events

Authors	Methodology	Selected findings
Arkin et al. (3)	Examined CIS CRF data, 1983-1991.	Cited numerous examples of CIS media campaigns substantially increasing call volume, including such campaigns as Asbestos Awareness, "Good News," Minority Cancer Awareness, Prostate Cancer Awareness, and selected smoking-cessation campaigns. News articles (e.g., about interleukin-2) and magazine stories also cited.
Anderson et al. (5)	Examined impact of President Reagan's diagnosis of colon cancer (1985) on CIS call volume; examined impact of training program to increase suggestions to consider clinical trials (1988) on the number of such suggestions recorded by counselors on CRFs. Compared the CIS before and after the designated event.	<ol style="list-style-type: none"> 1. President Reagan's diagnosis increased calls about colon cancer from 50 to 1250/day. 2. After CIS training program, counselor suggestions to consider clinical trials increased from 12 853 (1987) to 22 901 (1988). More than 36 000 estimated for 1990.
Stein (8)	Examined 1983 antismoking television PSA campaign involving U.S. Surgeon General Dr. C. Everett Koop. Campaign urged calls to the CIS. Also examined 1984 television PSA campaign targeting people 50+ years of age. Campaign urged calls to the CIS for information about cancer. Dr. Koop also served as spokesperson for this campaign. Data obtained from CIS CRFs.	<ol style="list-style-type: none"> 1. Smoking-related inquiries to the CIS rose from 600 per month (per regional CIS office) to 13 500. 2. Prior to campaign, 2800 calls per month nationwide from people 50+ years of age. Increased to 9000 calls per month during campaign.
Kean et al. (11)	Evaluated impact of 2-month radio campaign targeting rural population in Minnesota (1975). Campaign focused on promoting CIS number (Mayo Comprehensive Cancer Center). Pre- and postintervention telephone surveys used to assess impact of campaign.	<ol style="list-style-type: none"> 1. Prior to campaign, 74% of women said they practiced breast self-examination, compared with 79% after the pilot project. 2. Awareness of the CIS increased by 11% after campaign (42% versus 53%).
Parker et al. (13)	Examined impact on CIS call volume of two local campaigns targeting African Americans: 1) brochures at health fairs and stories in African American newspapers, 2) radio campaign. Examined CRF data from the CIS at Howard University.	<ol style="list-style-type: none"> 1. Print campaign had no effect on call volume from African Americans. 2. Radio campaign had substantial impact. Prior to campaign, African Americans represented about 10% of all calls. During campaign, increased over 50%.
Freimuth et al. (14)	Examined impact of several CIS campaigns on call volume nationally, 1983-1986.	CIS campaigns can dramatically increase call volume. Selected examples include 1) 1983 U.S. Surgeon General's antismoking campaign, 2) 1985 Aretha Franklin Cancer Prevention Awareness Campaign, 3) 1984-1985 Kellogg-NCI collaboration.
Brown and Potosky (26)	Examined impact of Reagan's colon cancer episode (1985) on 1) CIS call volume nationwide, 2) Medicare utilization rates of proctoscopy (Alabama, Connecticut, Washington, Wisconsin), 3) early-stage diagnosis of colon cancer (SEER* program).	<ol style="list-style-type: none"> 1. Substantial impact on CIS call volume. Baseline = 4% of all calls concern colorectal cancer; percentage increased to 16% during the month of Reagan's episode. Calls declined sharply 1-2 months after the episode but remained higher than baseline by about 300 calls nationwide per month through 1987. 2. Substantial increase in utilization of early detection tests at about the same time as Reagan's 1985 episode: 1983 = 34.7 (per 1000 beneficiaries); 1984 = 37.5; 1985 = 47.8; 1986 = 51.1. 3. Significant increase in detection of early-stage disease, from 3.6 per 100 000 (3-month period preceding Reagan's episode) to approximately 4.3 per 100 000 (during and immediately after Reagan's episode). Six months following Reagan's episode, early detection gains returned to baseline.

Table 4. Examples of studies assessing the impact of CIS promotion campaigns and/or unplanned events—Continued

Authors	Methodology	Selected findings
Cummings et al. (27)	A 52-week mass-media antismoking campaign targeting mothers with small children was implemented in seven media markets and compared with seven matched controls. Public was encouraged to call the CIS for information about quitting.	<ol style="list-style-type: none"> 1. Based on first 28 weeks of campaign, CIS call volume for smoking-cessation information was 10 times greater in intervention areas. 2. Purchased air time greatly increased call volume.
Pierce et al. (29)	Examined impact of three CIS antismoking television PSAs on CIS call volume (1984–1985). Compared call volume before, during, and after the television campaigns.	<ol style="list-style-type: none"> 1. Substantial increase in call volume, ranging from two- to ninefold increase. 2. Especially effective among males, callers under 40 years of age, and among the less educated. 3. Paid television time would have substantially increased coverage.
Jaén et al. (30)	Implemented and promoted smoking-cessation helpline within CIS in Buffalo, N.Y. Promotion lasted 15 months and included direct mailings, posters, newspaper articles, paid newspaper advertising, radio and television talk shows, paid radio advertising, and television PSAs.	<ol style="list-style-type: none"> 1. Approximately 2000 calls from current smokers, representing about 1% of all current smokers in target area. 2. Most effective promotion strategies (in rank order, most to least) included newspaper articles, television talk shows, radio talk shows, television PSAs, paid radio advertising, paid newspaper advertising. 3. PSAs were more effective in reaching younger, less-educated, non-White smokers. 4. Newspaper attracted a higher proportion of college-educated heavy smokers.
Adams (31)	Examined CIS national public-awareness campaign (1979) on hazards of asbestos exposure. Campaign relied on radio and television PSAs, print material, news releases. Program was evaluated using pre- and postintervention national telephone survey conducted by Gallup.	During campaign, 62% of adults surveyed indicated they had heard about asbestos hazards, compared with 50% prior to the campaign.
Bromley-Diaz (32)	Evaluated impact on CIS call volume of a 2-week pilot project (1979) designed to increase calls from Hispanics requesting smoking-cessation material. Television and radio PSAs and paid advertisements were used. A follow-up telephone survey determined how callers found out about the CIS. Study conducted in San Antonio, Texas.	Estimated 95 smokers called CIS. Majority of callers (66%) cited television as source, compared with 28% from newspapers and 3% from radio. Television more effective in reaching less educated smokers; newspapers more effective in reaching middle-class smokers. Television much more effective in reaching Hispanics.
Kotkiewicz and Moskowitz (33)	Evaluated impact of a subway advertising campaign in New York on calls to the CIS. Surveyed subway riders before/after the campaign.	<ol style="list-style-type: none"> 1. Prior to campaign, averaged 600 calls per month; increased to 1000 per month during campaign. 2. Knowledge of the CIS increased among White and African American female subway riders and among White and Hispanic male subway riders. 3. Reports of the subway being source of information about the CIS rose from last to first during campaign.
Girasek (34)	Examined impact of two published accounts of interleukin-2 on CIS call volume at Memorial Sloan-Kettering Cancer Center (Nov.–Dec. 1985). Two published articles appeared in <i>Fortune</i> magazine and <i>The New England Journal of Medicine</i> .	<ol style="list-style-type: none"> 1. Prior to articles, virtually no calls regarding interleukin-2. After publication of articles, calls increased to nearly 90 per week. 2. Three weeks after articles were published, call volume declined sharply and returned to near baseline.

Table 4. Examples of studies assessing the impact of CIS promotion campaigns and/or unplanned events—Continued

Authors	Methodology	Selected findings
Cummings et al. (35)	Examined impact of television promotion of NCI booklet "Diet, Nutrition and Cancer Prevention." Promotion occurred during four consecutive nightly broadcasts of the local news in the nation's largest television market (New York City, Long Island, southern New York state, northern New Jersey, Connecticut).	One of the largest responses in CIS history. Approximately 75 000 booklet requests attributable to television promotion (15 000 phone requests, 60 000 mail requests).

*Ed. note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to NCI on a computer tape. These computer tapes are then edited by NCI and made available for analysis.

Thompson et al. (39) also tested a telephone-based smoking-cessation protocol within the CIS. Although they did not find a difference between the two alternative telephone counseling protocols tested, they noted a self-reported quit rate that also compares favorably with previous research (19% quit rate at 1-year follow-up).

Also of relevance is another paper reported in this monograph, by Crosson et al. (40). These investigators report that enrollment in clinical trials at NCI increased dramatically following a special policy initiative and training program offered by the Office of Cancer Communications to increase dissemination of such information by CIS information specialists.

The studies cited above have examined the impact of the CIS on the behavior of callers. A related question concerns the behavioral impact of CIS mass-media campaigns within geographically defined populations, including people who do not call the CIS. Clearly, CIS mass-media campaigns can (and probably do) affect the behaviors of people who do not call the CIS. Unfortunately, knowledge about this broader, population-based impact of the CIS is sorely lacking in the research literature. One exception to this pattern is a study by Freimuth et al. (41) of the collaborative Kellogg Company-NCI All-BranTM advertising campaign. The investigators found that the 14-month national campaign substantially increased call volume to the CIS. For example, between November 1984 and December 1985, 20 000 calls to the CIS were triggered by this campaign, and over 30 000 written inquiries were received by the CIS. The investigators also report findings from two national surveys suggesting that an increase in the public's preference for bran and fiber occurred at about the same time as the campaign. Thus, in 1983 approximately 2% of the respondents to the National Cancer Prevention Awareness Survey said that they ate bran, fiber, and/or whole grain to reduce their cancer risk, compared with 5% in 1985 (during the campaign). Similarly, in 1984 (precampaign), approximately 9% of the respondents to the Food and Drug Administration-National Heart, Lung, and Blood Institute survey indicated that they ate fiber to prevent cancer, compared with 32% in 1986 (postcampaign). Finally, these investigators note that the Kellogg-NCI campaign apparently had a substantial impact on sales. In the first 24 weeks of the

campaign, there was a striking 47% increase in the market share of Kellogg's All-BranTM cereal, compared with an 11% increase for the most directly comparable brand.

Although the increase in fiber and bran consumption reported by Freimuth et al. (41) is suggestive, it is by no means conclusive evidence concerning the impact of the Kellogg-NCI campaign (e.g., the increase could represent a population-based trend that was occurring independently of the Kellogg-NCI campaign). The sales data, however, are much more convincing in this regard. Indeed, it is difficult to imagine an event or factor besides the advertising campaign that would be capable of triggering such a dramatic increase in the market share of the advertised cereal.

SUMMARY AND DISCUSSION

We began this paper by asking five key questions. On the basis of this review, we can answer each of these questions with substantial confidence (see Table 5). This review of the literature has also highlighted a number of areas that would benefit greatly from additional research. Six such areas are described below.

Estimating the Population-Based Impact of the CIS

It is almost inconceivable that after 15 years of service to the nation, we still do not know what impact CIS campaigns have within a defined population (i.e., their impact on callers as well as those who do not call the CIS). Unfortunately, this is precisely the situation that exists today in one of the premiere telephone information systems in the world. Such research would seem to qualify as a high priority, along with the collateral question of the extent to which CIS call volume can serve as a marker for population-based change (including changes in information-seeking behavior and subsequent behavior change that may result from this search for more information). In addition, such analyses should focus not only on the positive impact of the CIS (e.g., promoting behavior change conducive to cancer prevention and control) but also on potential negative side effects of providing such information (e.g., causing delays in seeking care).

Table 5. Major conclusions of literature review.

Question	Conclusions
1. Who uses the CIS?	The vast majority of callers to the CIS are female, White/Anglo, and of middle-class (or higher) background. Low-income populations and racial/ethnic minorities are underrepresented as users of the CIS. Approximately 40%–50% of calls are from cancer patients or friends/relatives of cancer patients. Some evidence suggests that cancer patients who call the CIS tend to be more sick and more stressed by their illness than cancer patients who do not call the CIS.
2. What are the topics of inquiry?	Most calls relate directly or indirectly to cancer-treatment issues. Topics of inquiry (at any given point in time) are especially sensitive to unplanned events and ongoing CIS promotional activity.
3. How do callers learn of the CIS?	A variety of media and sources are reported by CIS callers. Television ranks high across most studies. Some evidence suggests that print material may be less effective for minority and low-income populations, but culturally sensitive low-literacy print materials have not been adequately researched.
4. Do CIS campaigns and unplanned events affect CIS call volume?	CIS call volume can be substantially influenced by both unplanned events and CIS promotional campaigns. Evidence for this conclusion can be found in a variety of studies across time, at both the regional and national levels. More research should be encouraged on the use of low-literacy materials and radio for reaching underserved populations.
5. Can the CIS influence behavior?	The available evidence is overwhelmingly supportive of this hypothesis. Promoting calls to the CIS (information-seeking behavior) falls into this category and should not be taken lightly. Numerous studies have reported a positive CIS impact on self-reported health behavior. Two studies reported a positive impact on behavioral outcomes assessed independently of self-report (i.e., sales of high-fiber/bran cereal and enrollment in clinical trials).

Examining CIS Campaigns That Combine Community Outreach With Mass Media

Conspicuously absent from the research literature are well-designed, prospective intervention studies that combine the two major communication resources available to the CIS: mass media and community outreach. This line of research would seem to be especially timely given the recent addition of a community outreach coordinator in each NCI-funded regional CIS office (*1*). CIS campaigns that integrate and coordinate both of these resources may prove to be especially effective in reaching underserved populations.

Examining the Cost-Effectiveness of the CIS as a System for Disseminating Information

Analyses of cost-effectiveness of the CIS as an information-disseminating system, which are conspicuously absent in the research literature, might examine alternative methods for promoting the CIS in the mass media, using CIS call volume as the major end point or outcome measure (e.g., PSAs versus paid advertising), as well as comparing mass-media promotions with community outreach efforts with respect to increasing CIS call volume. This line of inquiry could, of course, be extended to cost-effectiveness with respect to behavior change (above and beyond information seeking as measured by call volume), although such research is likely to be quite expensive.

Examining CIS Campaigns That Target Low-Income and Minority Populations

The CIS continues to struggle with the problem of routinely reaching low-income and minority populations. The

persistence of this problem suggests the need for a sustained program of research, including phase III efficacy trials that have clear potential to evolve into phase V nationwide demonstration projects. Such research, as noted above, could focus on the combined effects of targeted and culturally sensitive mass-media and community outreach. Other potentially fruitful areas of research include exploring radio as a medium for reaching underserved populations and assessing the impact of low-literacy print materials on specific target audiences. Because systematic efforts by the CIS to promote cancer-control behaviors within special populations are still in their infancy, phase I (hypothesis development) and phase II (methods development) studies should also be given high priority. Such research is needed to understand the barriers and conditions that prevent special populations from engaging in cancer-control behaviors and also to identify effective media and other strategies for reaching these populations. In addition, the CIS is in an excellent position to work collaboratively with the NCI Division of Cancer Prevention and Control, the Centers for Disease Control, Division of Cancer Prevention and Control, as well as other national and regional agencies that are attempting to reach special populations. Such collaboration should be encouraged, supported, and coordinated at the highest levels of authority within NCI, the Centers for Disease Control, and other agencies and organizations as appropriate.

Examining CIS Campaigns That Target Primary and Secondary Prevention Behaviors

Information requests to the CIS clearly favor cancer treatment and related issues, an emphasis that is consistent

with the overall mandate of the CIS. The CIS, however, is also mandated to provide and disseminate information about primary and secondary prevention. There would appear to be substantial untapped opportunities for providing such information to CIS callers, especially in a proactive fashion (5,38).

Examining the Impact of the CIS on the Management of Cancer Patients

CIS telephone counselors routinely provide cancer patients and physicians with state-of-the-science information related to cancer treatment. Although, the extent to which this information actually influences clinical decision making is not known, the findings of Altman (36) and Manfredi et al. (6,37) clearly are suggestive in this regard. Because cancer patients constitute a key target audience of the CIS, more research of this issue should be encouraged, especially as a strategy for improving the use of this information by cancer patients and physicians. Also lacking in the research literature are studies examining the awareness and attitudes of health-care professionals (e.g., primary-care physicians, medical oncologists) regarding the CIS. There would seem to be significant untapped opportunities to conduct such research (including intervention research) within NCI-funded clinical cooperative groups.

CONCLUSION

In short, this review of the literature has shown that the CIS is a viable laboratory for communications research. What is particularly striking is the sheer volume of research that has been generated over the past 15 years—all the more remarkable when the lack of extramural support for much of this research is taken into consideration. Missing from this body of research, however, with few exceptions, is a well-conceived program of phase I–II research, as well as phase III intervention research that is prospective in design and grounded in behavioral science and/or communications theory. The Cancer Communications Systems Research initiative (described above) provides an excellent precedent for such research. More research initiatives of this type should be encouraged, especially as a strategy to guide future program planning and protocol development by the CIS.

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Narrowing the Cancer Knowledge Gap Between Whites and African Americans

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The results of three studies are reported, all of which explore the cancer knowledge gap between African Americans and Whites and the cancer information-seeking behavior of African Americans. In study 1, 5000 randomly selected Call Record Forms from African American and White callers to the Cancer Information Service (CIS) were analyzed to compare characteristics of callers and motivations for information seeking. In study 2, 54 in-depth interviews were conducted with African American callers recruited from five CIS offices to explore the callers' motivations for information seeking and the quality of their experience with the CIS. Study 3 was a random-digit dial survey of 601 African American residents of the District of Columbia and Prince George's County, Maryland, to assess their cancer knowledge, attitudes, and behaviors as well as their use and trust of information sources. In study 1, we found that African Americans who called the CIS were very similar to the White callers in two respects: their educational levels were particularly high, and most were female. Proportionally more African Americans, however, were general-public callers, and fewer African Americans than Whites were classified as family or friends of patients. In study 2, we found that most of the African American callers, originally classified as general-public callers, actually were family members of cancer patients or symptomatic individuals. Typically, they were quite satisfied with their information-seeking experience; most of them followed the behavioral suggestions given in the phone call. In study 3, we found further evidence of a knowledge gap (measured by education) within the African American community. Those respondents with the most education were also more knowledgeable about cancer, held the most positive attitudes toward the disease, and more frequently practiced most of the recommended behaviors. Television continued to emerge as the most important source for cancer information and awareness of the CIS. [Monogr Natl Cancer Inst 14:81-91, 1993]

INTRODUCTION

To meet the National Cancer Institute's (NCI's) year 2000 goal of reducing cancer deaths by 50%, groups in society that are underinformed and underserved will need to be reached more effectively. The group most underserved is the poor, and a disproportionate number of African Americans are poor. Because seeking and un-

derstanding information about cancer is one of the earliest steps in improving prevention, detection, and treatment behaviors, the present report focuses on exploring the reasons for the cancer knowledge and service gaps that exist between Whites and African Americans and identifying effective strategies to reduce these gaps.

A federal task force on African Americans and minority health reported in 1986 that nearly 60 000 excess deaths a year occur among African Americans (1). "Excess deaths" are defined as deaths that would not occur if the mortality rate were the same for Whites and African Americans. This gap between Whites and African Americans results in higher death rates for African Americans for several types of cancer—lung, 45% higher; prostate, twice as high; esophagus, three times as high; and cervix, two and one-half times as high (1). Of the 24 most common cancers, 18 are more prevalent in African Americans than in Whites (1). African Americans have the highest overall age-adjusted rates of cancer incidence and mortality of any U.S. population group (1).

Moreover, surveys consistently find that African Americans are less knowledgeable than Whites about most cancer-related issues (2-4). These early studies suffer from a common sampling problem, however. A cross section of the minority population needs to be studied rather than only its lowest socioeconomic stratum. In large national probability samples, African Americans are often oversampled by locating census blocks which are primarily African American (i.e., often the urban ghetto areas) and concentrating interviewers in these areas. The result is frequently an overrepresentation of the lowest classes and an absence of middle- and upper-class African Americans. Consequently, it is difficult to separate the effects of low socioeconomic status from the effects of race.

The earlier surveys cited above do not allow us to address an important question: Are these knowledge gaps attributable to race or to socioeconomic status? None of these surveys had sample sizes sufficiently large to allow separate analyses for socioeconomic status levels. Two studies were found that addressed this issue indirectly. In a 1977 household survey, conducted as part of the Los Angeles Health Survey, scores from 25 questions were combined to determine general cancer knowledge level (5). This study supported the influence of ethnicity on cancer knowledge. Even after controlling for education, behavior, and cancer worry, African Americans had signifi-

*See "Notes" section following "References."

cantly lower levels of knowledge than Whites, Asians, and others.

The most recent examination of this issue comes from an analysis of the 1987 National Health Interview Survey Cancer Control Supplement (6). This analysis examined four behaviors related to cancer prevention: diet change, mammography utilization, fecal occult blood test utilization, and smoking. Predictor variables included race, sex, age, income, dietary concerns, and four knowledge-related variables: education and three measures of cancer prevention knowledge. Race was a significant predictor by itself for all the dependent variables except smoking status among women. When other demographic and knowledge-related variables were added, however, race was no longer a significant predictor.

These two studies suggest that cancer knowledge is an important intervening variable between race and preventive behavior change, making it even more critical to understand the differences in cancer information seeking and processing for African Americans and Whites and leading to the following objectives of this research:

- Assess the extent and nature of the cancer knowledge and service gaps between Whites and African Americans.
- Study those African Americans who have been cancer information seekers to learn more about their characteristics, motivations, and experiences.
- Assess potential channels for reaching African Americans with cancer information.

Three studies were completed to meet these research objectives. In study 1, 5000 randomly selected Call Record Forms from African Americans and White callers to the Cancer Information Service (CIS) were analyzed to compare characteristics of callers and motivations for information seeking. In study 2, 54 in-depth interviews were conducted with African American callers recruited from five CIS offices during 1988 and 1989 to explore their motivations for information seeking and the quality of their experience with the CIS. Study 3 was a random-digit dial survey of 601 African American residents in the District of Columbia and Prince George's County, Maryland, to assess their cancer knowledge, attitudes, and behaviors as well as their use and trust of information sources. In the following sections, the methodology and results for each of these studies are described.

STUDY 1: DIFFERENCES BETWEEN AFRICAN AMERICAN AND WHITE CALLERS

Methods

This phase of the research examined differences in the cancer information-seeking behavior of African Americans and Whites by analyzing call-record data from a random sample of 5000 African American and White callers to the CIS. Each of the more than 1.5 million calls to the CIS placed between 1983 and 1986 has been documented on a standard Call Record Form, which records information on type of caller, the nature of the inquiry, the cancer sites discussed, behavioral suggestions given to

the caller, and referrals to physicians, clinical trials, and community resources. In addition, information about the caller is obtained, including the following: 1) previous use of the CIS, 2) how the caller learned about the CIS, and 3) demographic data (age, sex, education, ethnic background, and location) (7).

Results

Demographic differences between African American and White callers. The CIS is used primarily by Whites; in fact, almost 88% of the CIS users are White, although this group constitutes 80% of the U.S. population. African Americans constitute 7.6% of CIS users and 11.5% of the U.S. population. These figures suggest that not all population subgroups are using the CIS equally. For this analysis, a random sample of 5000 African American and 5000 White cancer information seekers was selected from the larger database.

As Table 1 shows, there are some racial differences¹ in type of callers.

White information seekers are more likely to be cancer patients or families/friends of cancer patients; African American information seekers are more likely to be symptomatic individuals or members of the general public. It is difficult to understand the reasons for these differences. There were, however, several public service prevention campaigns directed at African American audiences during this period that may have inflated the proportion of general-public calls.

Table 2 shows that there are educational differences between African American and White callers.

The most educated persons of both races are the ones most likely to use the service. Proportionately more African Americans who have less than a high-school education use the service than do Whites. The proportions of African American and White users who have high-school diplomas or some college are about equal. Not until college graduates are compared does the proportion of White users exceed that of African American users.

There are some age differences between African American and White callers. For the youngest callers (age 18-39), proportionately more African Americans use the information service (9%) than do Whites (7%), but after age 40 that trend is reversed (i.e., 18% of White and 16% of African American callers are in the 40-49 age group;

Table 1. Type of caller by race (CIS, 1983-1986)

Type of caller	Whites, % (n = 4777)*	African Americans, % (n = 4612)*
Patient	11	7
Family of patient	21	12
Symptomatic/no doctor	3	6
Symptomatic/doctor	3	4
General public	58	68

*Percentages do not total 100 because some callers, such as health-care professionals, were not included and other callers could not be classified by type.

Table 2. Education of callers by race (CIS, 1983–1986)*

Education level	Whites, % (n = 4978)	African Americans, % (n = 5101)
Grade school	4	4
Some high school	7	13
High-school graduate	33	32
Some college	26	29
College graduate	20	13
Postgraduate	8	6

*Missing data = 2% for Whites, 3% for African Americans. Numbers of callers differ because demographic data are not complete for every caller.

16% of White and 11% of African American callers are 50–59 years old; and 17% of White and 7% of African American callers are 60 years and older).

There are no differences between races in the distribution of calls based on gender. Both African American and White women call three times as often as do men.

Differences between African American and White callers in source of information about the CIS. Table 3 shows how African American and White callers differ in the way they first learned of the CIS. As indicated, the relative ranking of the various sources of information is virtually identical for African American and White callers.

African American users, whether patient, symptomatic, or general public, were somewhat more likely to learn of the service from television than were White users. In contrast, the American Cancer Society (ACS) and print media (e.g., brochures, newspapers) were cited somewhat more frequently by Whites than by African Americans. An example of the importance of television for the African American audience comes from an analysis of a video news release featuring singer Patti LaBelle which was used in the 1991 National Minority Cancer Awareness Week campaign. The California CIS office reported that their usual 9% of calls from African Americans increased to 26% during that campaign (8).

Differences between African American and White callers in what they asked about. There are seven body sites where African Americans experience excess mortality from cancer: lung, esophagus, stomach, pancreas, pros-

tate, cervix, and corpus uteri (1). Table 4 shows the comparison between proportions of African Americans and Whites calling about these body sites.

African American callers asked proportionately more often about only three of the seven sites for which they suffer excess mortality (i.e., stomach, cervix, and uterus), and these differences were quite modest.

For each call to the CIS, up to five different subjects of inquiry can be coded from a checklist containing 56 different codes. For the vast majority of the 56 subjects of inquiry, there were no differences between White and African American callers. Table 5 reports the subjects of inquiry in which there was at least a 2-percentage-point difference between Whites and African Americans.

These differences seem to follow the patterns for type of caller. Because more White callers were patients or families of patients, they also asked proportionately more often about physician referral, body-site information, diagnosis, treatment, chemotherapy, and clinical trials. African American callers were more often identified as general-public callers and consequently asked more often about prevention, symptoms, smoking, publications, and cancer in general.

Differences in the way the system responded to African American and White callers. As shown in Table 6, for most of the behavioral suggestions examined, there were no differences between Whites and African Americans within each of the three major caller groups (i.e., patients, symptomatic callers, general public). In those cases where differences were statistically significant, the magnitude of the difference was generally quite modest. The largest differences occurred with respect to suggestions to call the NCI among patients (Whites = 19%; African Americans = 14%) and suggestions to read literature among the general public (Whites = 50%; African Americans = 46%).

Additional analyses examined the time spent on the telephone with White and African American callers. Sixty-nine percent of the White callers had calls lasting 1–5 minutes, compared with 76% of the African American callers. At the other end of the continuum, however, involving calls in excess of 15 minutes, virtually identical percentages were found, with 6% of Whites and 4% of

Table 3. Major source of information about the CIS by race (CIS, 1983–1986)

Source	Whites, % (n = 4979)	African Americans, % (n = 5127)
Television	12	15
Telephone book	8	7
Friends/relatives	7	6
American Cancer Society	7	3
Brochures	6	4
Newspapers	4	2
Magazines	3	2

Table 4. Calls about specific body sites by race (CIS, 1983–1986)*

Body site	Whites, % (n = 2003)	African Americans, % (n = 1494)
Lung	11	11
Esophagus	1	1
Stomach	1	3
Pancreas	2	2
Prostate	4	4
Cervix	3	5
Corpus uteri	2	3

*Includes only those body sites for which African Americans have excess mortality (1).

Table 5. Selected subjects of inquiry by race (CIS, 1983-1986)

Subject of inquiry*	African Americans, %	
	Whites, % (n = 4858)	Americans, % (n = 4864)
Publications	38	42
Smoking	21	26
Prevention	21	23
Body-site information	14	10
Symptoms	6	9
Physician referrals	5	3
Treatment	5	2
General cancer questions	5	7
Diagnosis	4	2
Clinical trials	3	1
Chemotherapy	3	1

*The Call Record Form permits the CIS specialist to record up to five subjects of inquiry coded from a list of 56. This table lists only those subjects where the difference between Whites' and African Americans' inquiries differed by at least 2 percentage points.

African Americans experiencing such calls. It would appear that at least some of this difference in length of call can be explained by racial differences in type of caller. For example, as Table 7 shows, when length of call between White and African American callers was examined among general-public callers (i.e., the largest caller group), time spent on the telephone was virtually identical for the two groups.

With respect to symptomatic callers and patients who called the CIS, significantly more African Americans than Whites experienced calls of 1-5 minutes (47% of the African Americans to 38% of the Whites for patients, and 56% of the African Americans to 47% of the Whites for symptomatic callers). It is unclear at this time why these differences in length of call exist. It is important to note, however, that the length of the call is not simply a function of the CIS information specialist. Providing information over the telephone is fundamentally interactive by nature. Thus, if African American callers are less comfortable interacting on the telephone with the CIS infor-

mation specialists, if they ask fewer follow-up questions or are less likely to mention multiple subjects of inquiry, these nuances in the communication process could significantly affect the length of time spent on the telephone. As will be noted in study 2, there is evidence to suggest that African American callers may indeed be less likely to disclose information over the telephone, which may account for some of these differences in call length. Clearly, more research is needed to examine this potentially significant issue.

STUDY 2: INTERVIEWS WITH AFRICAN AMERICAN CALLERS

Methods

Because the data collected on the Call Record Forms are somewhat limited, more information was needed to understand fully African Americans' motivation for using the service and their evaluation of the experience. We used five different offices across the country, selected on the basis of their volume of African American calls, to recruit participants for this phase of the study. The Maryland, Illinois, Michigan, Alabama, and Florida CIS offices recruited a total of 60 African American callers over a period of 9 months during 1988 and 1989.

Two African American female graduate students who had been on the staff of the research project were trained as interviewers. Fifty-four interviews were completed out of the possible 60 names available. Interviews that were not completed were the result of inaccurate telephone numbers or unavailability of the person rather than the callers' refusal to be interviewed. The interviews took place during June and July 1989. Transcripts were made of each interview.

Results

Motivations for cancer information seeking. Even though all of these 54 callers were classified as general-public callers on the Call Record Form at the time of the call, in the follow-up interview, about half said they had

Table 6. Behavioral suggestions given by type of caller by race of caller (CIS, 1983-1986)*

Suggestion given	Patients†			Symptomatics†			General public†		
	W, % (n = 1492)	AA, % (n = 849)	P‡	W, % (n = 366)	AA, % (n = 474)	P‡	W, % (n = 2827)	AA, % (n = 434)	P‡
Read literature	39	36	NS	29	24	NS	50	46	.002
Visit doctor	27	27	NS	45	51	NS	3	3	NS
Share information	11	11	NS	4	3	NS	6	4	<.001
Call hospital	6	7	NS	8	11	NS	3	4	.04
Call ACS	7	9	NS	4	1	.004	2	2	NS
Call NCI	19	14	.002	8	6	NS	3	3	NS

*W = white; AA = African American; NS = not significant.

†Columns total more than 100% because several suggestions to callers can be recorded on the Call Record Form.

‡Based on chi-square tests, with 1 degree of freedom.

Table 7. Length of call by type of caller by race of caller (CIS, 1983-1986)*

Length of call, min	Patients†			Symptomatic†			General public†		
	W, % (n = 1433)	AA, % (n = 824)	P‡	W, % (n = 350)	AA, % (n = 456)	P‡	W, % (n = 2737)	AA, % (n = 3043)	P‡
1-5	38	47	<.001	47	56	.019	89	89	.317
6-15	46	42		43	38		10	9	
15+	15	10		10	6		1	1	

*W = White; AA = African American.

†Columns do not always total 100% because of rounding.

‡Chi-square tests, with 2 degrees of freedom.

called because they had a family member or friend who had cancer or they had symptoms they were concerned about. This discrepancy suggests that African American callers may be somewhat reluctant to disclose the real reasons for their calls to the CIS information specialists.

About one fifth of the callers were interested in smoking cessation and were looking for specific programs in their area, encouragement, and/or tips to quit smoking. Several callers labeled themselves "health nuts" and said they were "interested in prevention" or just "always looking to be more knowledgeable." The remaining callers had specific motivations such as looking for a special recipe book, requesting pamphlets for a health fair, or doing a school project.

Source of information about the CIS. Consistent with other data reported here, over half of the interviewees said they had first heard of the CIS through commercials on television. Many of these callers reported that they called immediately after seeing the televised spot, supporting the importance of the public service announcement as a cue to action for information seeking. Several others heard of the CIS from radio or newspaper advertising. Pamphlets were a source of information for several; they reported that they got these pamphlets from grocery stores, health fairs, or schools. Two callers had first contacted ACS and learned of the number there, and three callers had used directory assistance or the telephone book.

Sixteen callers said they had called the CIS before asking a doctor for information; six had spoken to their doctor first. The rest of the callers had talked to friends or family or had done reading on their own (library, encyclopedia, pamphlets) before calling.

Evaluation of their CIS experience. All but two of the 54 callers interviewed felt that the information specialist was understanding, encouraging, caring, supportive, and polite. No one complained about how long it took to get through. Only two people complained that the materials requested did not arrive. One had been waiting 2 weeks and the other, 1 week.

Seven callers complained that the information specialist did not answer their questions completely and did not appear knowledgeable. Two of these callers had specific symptoms and sounded as though they wanted a telephone diagnosis. The following quotation is from one of these dissatisfied callers: "I asked him a couple [questions] and then he just told me that he was not a doctor and he could

not answer questions, but he would send me information."

Almost everyone said the hours for telephone service should be longer. The majority suggested that the service should be available until 8 or 9 PM. A few strongly advocated a 24-hour service. The following comment summarizes the arguments given for extended hours:

Well, most people work, so in any situation like that I think weekends or evenings are better because, especially Blacks, they have to work for a living. There are very few Blacks who are independently wealthy, so it should be available to them at a time when they have the time to go or to seek, so I would say evenings and Saturdays.

Action taken following the call. Most of the callers reported reading or at least skimming through the materials they received. About one third of the callers shared the information with co-workers, family, and friends. Two of the 54 interviewed reported going for a physical exam or mammogram after reading the information. Several callers said they had changed their diet to include more produce and fiber. The only negative comment came from one male who said he threw everything away without looking at it.

Recommendations for reaching African Americans. The interviewers asked callers for their recommendations on effective ways to reach the African American audience with cancer information. Several suggestions were given, a number dealing with mass-media messages. It was suggested that African American radio stations be used more often.

African American magazines were a source of information that seemed to be popular with these callers. They mentioned *Ebony*, *Jet*, and *Essence*. In general, the callers recommended using a wider variety of media sources and saturating the African American community with this information.

Several comments concerning the advertisements about cancer and the CIS seemed to criticize them for not being targeted more specifically to African Americans. Callers said that the information needs to focus on them. They suggested that longer television programs be produced, such as documentaries that are aimed at African Americans and have statistics about African Americans and cancer. The following quotation reinforces this need to target information:

... because we don't want to hear something that really doesn't affect us. You know, we want to hear something that is going to like deal exclusively with us like, you know, some of the cancers that are really heavy in Black communities.

In addition to personalizing the mass-media messages, there were many suggestions about the need to use interpersonal strategies to reach African Americans. For example, several callers recommended that information be distributed by people in grocery stores so that there would be a personal appeal to read the material or change the behavior. They also recommended that groups in the African American community be mobilized to assist with the effort. One caller suggested specific organizations, such as the Black Chamber of Commerce, African American professional organizations, and African American medical associations. There seemed to be an emphasis on face-to-face activities, such as lectures and smoking-cessation programs.

Although not discussed directly, there were references to a stigma associated with cancer, a reluctance to talk openly about it—a stigma that inhibited the flow of information, the interviewees believed.

In short, these African American callers were motivated to call the CIS because of their exposure to the cancer of a loved one, their own symptoms, or a media message that caught their attention. They were quite well satisfied with the experience. They did not report feeling alienated or rudely treated by the information specialists. There was some evidence that they did not disclose much information about the real reason for the call, and that reticence might have made it difficult for the information specialists to help them as much as they could.

Even though they were quite satisfied with their own experience, these callers were not at a loss for recommendations on reaching African Americans more effectively. Most of their suggestions, although not expressed exactly this way, called for more targeting to the African American community and more personalization of the messages.

STUDY 3: SURVEY OF AFRICAN AMERICANS

Methods

African American adults, 18 years or older, in the District of Columbia and Prince George's County, Maryland, were surveyed in January and February 1989 utilizing computer-assisted telephone interviewing by the University of Maryland Survey Research Center. All interviews were conducted by African American interviewers. Sampling was based on a probability sample of telephone prefixes of the target areas (i.e., the District of Columbia and Prince George's County, Maryland), followed by four random digits. The conventional random-digit dialing methodology (9) was modified using the Blair and Czaja (10) technique to more efficiently reach a special population. At least five callbacks were tried before a number was abandoned. Further, numbers were abandoned if it

was determined that they were not African American residences or were non-residences (e.g., places of business). Of the 813 households sampled, 601 interviews were completed (i.e., a 74% response rate).

Results

Description of the sample. Table 8 shows the demographics for the weighted and unweighted sample compared with available census data on African Americans.

Table 8. Demographics of the sample compared with population figures (CIS, 1983–1986)

Parameter	Sample		U.S. census of African Americans, %
	Unweighted, % (n = 601)	Weighted, % (n = 624)	
Sex			
Male	39	46	47*
Female	61	54	53
Education			
Some high school	12	35	NA†
High-school graduate	34	36	35.6‡
Some college	27	17	—
College graduate	16	8	12
Postgraduate work	6	2	
Postgraduate degree	6	2	
Income			
Under \$5000	3	6	13.5§
\$5000–\$9999	4	7	17.1
\$10 000–\$14 999	6	9	14.3
\$15 000–\$24 999	16	16	22.0
\$25 000–\$34 999	18	16	58
\$35 000–\$49 999	30	26	
\$50 000–\$74 999	14	11	
\$75 000 +	7	5	NA
Don't know	2	4	NA
Age, y			
18–24	13	14	NA
25–34	30	24	NA
35–44	26	22	NA
45–54	14	14	NA
55–64	7	9	NA
65–74	5	11	NA
75 +	5	6	NA
Marital status			
Single	40	37	41
Married	39	37	35
Divorced	10	10	8
Widowed	6	10	8
Separated	5	7	9

*Data from U.S. Bureau of the Census, 1988 (pers. com.).

†NA = not available.

‡Data from U.S. Bureau of the Census, 1986 (pers. com.).

§Data from U.S. Bureau of the Census, 1985 (pers. com.).

Because the sample was skewed toward females and higher educational levels, the results were weighted on both these variables. The maximum weight for a single case was 3. The weighted sample matches the available population figures reasonably well except for income. The incomes reported for the sample are higher than available census figures for income. These available census figures are from 1985, however, and are for the African American population of the entire United States. The metropolitan Washington, D.C., area has a relatively high income level.

Because level of education was hypothesized to be an important predictor of cancer knowledge and attitudes, all of the findings were analyzed for educational differences. The code for education was collapsed into three categories: less than a high-school diploma, high-school graduate, and some college and above. Statistically significant educational differences are indicated in Tables 9-11 and will be discussed in the interpretation of the table.

Knowledge and attitudes about cancer. A number of questions were asked of the African American respondents to assess their level of concern, knowledge, and attitudes regarding cancer and its treatment. First, respondents were asked to list unaided those diseases they felt were most serious for African Americans in general; a more specific question followed, asking what diseases they felt were most serious for them. For each of these questions, they were asked to give three different responses. Sixty-five percent of the respondents listed AIDS as the disease most serious for African Americans generally, and 32% identified this disease as most serious for them personally. Cancer rates highly in both lists and is, in fact, the number-one disease that African Americans report as being the most serious concern for them.

Another set of questions on the survey explored the issue of African Americans' perceived susceptibility to cancer and perceived efficacy in reducing one's chances of

getting cancer. Table 9 shows the results from three relevant questions.

The dagger in Table 9 indicates that there were significant educational differences in the responses to the question asking if there were anything one could do to reduce the chances of getting cancer. The direction of the educational differences was somewhat unexpected. High-school graduates were significantly less likely than those with both less and more education to believe they could reduce their chances of getting cancer. It is also important to note that there were no educational differences in the perceptions of the likelihood of developing cancer in their lifetimes.

To assess knowledge, respondents were asked, "What would you say are the early signs of cancer?" Answers were judged correct if they conformed to the seven early-warning signs of cancer publicized by ACS. Respondents were probed for up to three responses. In general, this sample could name less than one warning sign (an average of 0.75). There were significant differences in knowledge of these warning signs across educational levels, with the least educated respondents giving the fewest correct answers, for an average of 0.65. Even those with some college, however, were on the average able to name only one early-warning sign.

Respondents also were asked, "What do you think a person can do to reduce his or her chances of getting cancer?" Some common health-promoting behaviors given included avoiding use of tobacco and alcohol; eating less fat and red meat and more fiber and cereal; avoiding x-ray exposure, the sun, and stress; and getting adequate exercise and sleep. Again, respondents were probed for up to three responses. On the average, only 1.29 answers were given. This finding also varied systematically by education level, i.e., the more education, the more health-promoting behaviors were given. The most educated third of the respondents gave an average of 1.52 responses.

Attitudes toward cancer were assessed with a series of eight Likert item opinion statements that asked respondents to respond on a five-point scale. Table 10 shows the

Table 9. Perceived susceptibility to cancer by African Americans (1989 Minority Cancer Survey, weighted n = 624)

How likely do you think it is that you will develop cancer in your lifetime?	
Fairly likely:	34%
Not too likely:	26%
Not likely at all:	25%
[No response]	[15%]
Why do you think you will develop cancer?*	
Family history:	32%
Lifestyle:	28%
Matter of fate:	9%
What do you think a person can do to reduce his or her chances of getting cancer?	
There is something a person can do:	77%†
Eat healthy:	58%
Avoid smoking:	55%
Exercise regularly:	20%

*More than one response could be given. Only responses occurring frequently are included in the table.

†Significant differences across educational levels.

results for these attitude items. For Table 10, the responses were recoded so that "strongly agree" and "agree" were combined and "strongly disagree" and "disagree" were combined.

Even though these results demonstrate that large proportions of the respondents are expressing more positive attitudes toward cancer, there remain substantial numbers of African Americans who believe that cancer is a death sentence, that the treatment is worse than the disease, and that everything causes cancer. There were significant educational differences for the five statements marked with an asterisk on Table 10. In all cases, the least educated group responded the most pessimistically.

Because there are significant differences in cancer incidence and mortality between African Americans and Whites, we asked respondents about their perceptions of these differences. They were asked whether African Americans or Whites were more likely to get cancer and more likely to be cured of cancer. Twenty-eight percent of the African American respondents believed that African Americans were more likely to get cancer, and 25% felt that Whites were more likely to be cured.

The majority of the African American respondents appeared to be unaware of the statistical disparity in cancer incidence and mortality between African Americans and Whites. This result is surprising because considerable publicity has appeared in the Washington, D.C., metropolitan area highlighting these differences. The District of Columbia has even been called the "cancer capital of the world." There were statistically significant differences in the educational level of respondents to the question about cancer cure. Instead of the usual pattern of least-educated groups being the most pessimistic, in this case it was the more-educated respondents who thought African Americans were less likely to be cured of cancer. Perhaps the more-educated respondents had been more exposed to the publicity on this issue.

Potential channels for dissemination of cancer information. Another major objective of the survey was to analyze the use and credibility of different channels of communication by the African American audience. First, we assessed the patterns of use of various mass-media channels. Most of the respondents reported reading a newspaper more than once a week. A general-audience newspaper was read more frequently than African American newspa-

pers. African American magazines were read by over three fourths of the sample. Again, more than three fourths of the respondents had read a health pamphlet. The only educational differences that were statistically significant were for newspaper and health pamphlet readership, and they were in opposite directions. A larger proportion of the less-educated respondents reported reading newspapers frequently. On the other hand, fewer less-educated African Americans reported ever reading health pamphlets.

A similar analysis was done for African Americans' use of broadcast information sources. For the overall sample, the average number of hours spent watching television daily was 4. This average did vary significantly by educational level. The more-educated group spent less time watching television. Ninety percent of the sample reported that they watched African American shows or stations. When asked specifically what these were, some of the frequent responses included "The Cosby Show," channel 32 (a local Public Broadcasting System station with predominately African American programming), Black Entertainment Television, and "A Different World."

African Americans' use of interpersonal information sources also was assessed. We asked, "Do you have conversations with family, friends, and people at work concerning health issues?" Eighty-eight percent of the sample reported health-related conversations with family, 70% with friends, and 59% with co-workers. There were significant education-level differences for all of these interpersonal sources. The more-educated respondents were more likely to report having health-related conversations with all three sources.

In addition to amount of use, we also were interested in the relative credibility of these information sources for health information. We asked respondents to rate degree of trust they felt for health information coming from each of the sources. The ratings were made on a 4-point scale with 1 being a great deal, 2 somewhat, 3 a little, and 4 not at all.

The average rating of trust is high across all information sources but is highest for health pamphlets, African American television, and family sources. Friends and co-workers are the least-trusted sources. There are significant educational-level differences for African American newspapers, health pamphlets, and radio. In all three cases, the most-educated group is most trusting of the source.

Table 10. Attitudes toward cancer by African Americans (1989 Minority Cancer Survey, weighted n = 624)

Attitude	Agreeing, %	Disagreeing, %	Not sure, %
Cancer is a death sentence.*	39	49	12
Chances of a cure are better now.*	84	9	7
Cancer treatment is worse than the disease.	27	45	28
Early treatment helps cure cancer.	86	6	8
It seems everything causes cancer.	43	44	13
Not much can prevent cancer.*	32	58	10
Good health is a matter of good luck.*	32	65	3
To test early is to look for trouble.*	10	85	5

*Significant differences across educational levels.

Community groups are another potential channel for disseminating cancer information. We asked the respondents if they participated in several types of groups. Slightly more than half of the sample reported participating in church groups. No other group had more than a 30% participation rate. For three of the groups, participation was directly related to amount of education. The more educated the person, the more likely he or she participated in school, professional and business, and work site groups. For the social and community groups, high-school graduates were the least likely to participate, followed by those with less than a high-school diploma and those with some college.

In addition to general channels, we evaluated the awareness, use, and trust of specific cancer information sources. Three sources were evaluated: ACS, NCI, and the CIS, identified both by name and by its publicized telephone number, 1-800-4-CANCER. In addition to these sources, we asked about a fictitious source, the Williams Cancer Center, to help us judge how much overreporting of awareness and use we were getting.

Thirty-three percent of the respondents reported that they had made a special effort to get cancer information in the past. There were significant differences across educational levels. Those with high-school diplomas were the least likely to report seeking cancer information, followed by the least-educated group; the college-educated group was the most likely to seek information. Table 11 shows that there is a small overreporting problem in that 7% of the sample may be responding inaccurately, suggesting that the other estimates may be inflated somewhat. The cancer information source with the highest level of awareness is ACS followed by NCI and then the CIS. Awareness of the CIS is reported consistently whether the service is referred to by its name or its telephone number. The only education-related difference among respondents' awareness is for NCI. Less-educated respondents are less likely to be aware of NCI.

Only a small percentage reported contacting any of these information sources. Ten percent report contacting ACS. The college-educated group contacted most often, followed by the less than high-school educated group and the high-school graduates. The same educational pattern

was found for contacts with NCI. Nine percent reported contacting the CIS, and 8% reported using the 1-800-4-CANCER telephone number, but these percentages may not be strictly additive.

The average trust ratings shown in Table 11 reveal that ACS is trusted the most, followed by NCI and the CIS. It is interesting to note that the CIS has a higher trust rating when it is referred to by name than it does when it is identified by its telephone number. This finding raises an interesting question about the perception of information from a telephone number. For three of these trust ratings, there were significant educational differences: ACS, NCI, and the 1-800-4-CANCER number. In each of these cases, the less education, the less trust.

CONCLUSIONS AND RECOMMENDATIONS

My conclusions and recommendations are organized according to the three objectives for the research project.

Assessing the Extent of the Gaps

The results from all phases of the research document the existence of a cancer knowledge and service gap between Whites and African Americans. African Americans are more likely to get cancer and much more likely to die from it than Whites. They are less likely to know early-warning signs, to believe that cancer can be prevented, and to use information services such as the CIS. They engage in more risky lifestyle practices, such as smoking, than do Whites. Yet, there are surprising contradictions to these patterns. In some studies, African Americans are more likely than Whites to be aware of such detection practices as breast self-examination and such preventive practices as eating better.

The survey phase of this research demonstrated that the socioeconomic class differences (as measured by education) among African Americans do affect their knowledge, attitudes, and practices regarding cancer. Education is an important predictor of the extent of the knowledge and service gaps. The least-educated African Americans in the sample experience more of a cancer knowledge gap than the more-educated African Americans. Yet, previous

Table 11. Awareness, use, and trust of cancer information sources by African Americans (1989 Minority Cancer Survey, weighted n = 624)

Information source	Heard of, %	Contacted, %	Average trust*
ACS	94	10†	1.83†
NCI	77†	7†	1.94†
CIS	35	9	2.00
1-800-4-CANCER	36	8	2.14
Williams Cancer Center (a fictitious source)	7	6	2.00

*The lower the number, the higher the trust rating.

†Significant differences across educational levels.

research as well as qualitative research conducted for this study suggest that better-educated African Americans are not necessarily the same as their White counterparts. Apparently, cultural differences, regardless of socioeconomic similarities, influence knowledge, attitudes, and practices regarding cancer.

Changing the educational level of African Americans is beyond the role of cancer-information communicators, but these results suggest an alternative strategy. A structural equation model was developed and tested to explain the causal relationships among such demographic characteristics as age, sex, education, income, cancer knowledge, perceived susceptibility, pessimistic attitudes about cancer, and cancer information seeking (11). These results add further evidence to the existence of a knowledge gap between Whites and African Americans regarding cancer. They also reinforce the detrimental consequences of that gap by showing that cancer knowledge directly predicts information seeking. These findings also suggest that perceived susceptibility, although not related directly to cancer knowledge, also predicts information seeking. This finding may suggest another strategy for interventions designed to reduce the cancer knowledge gap. By increasing the perception of susceptibility to cancer, African Americans, regardless of educational level, may experience increased motivation to seek more information about cancer.

African American Cancer Information Seekers

Most African Americans who use the CIS are female and well educated. They are most often classified as general-public callers, although there is some evidence that they may disclose less about the real reason for their calls and, thus, may be labeled inaccurately. African American callers learn about the CIS more frequently from television and less frequently from ACS and the print media than do Whites.

African American callers asked proportionately more often about only three of the seven sites for which they suffer excess mortality—stomach, cervix, and uterus. African American callers asked more frequently about prevention, symptoms, smoking, publications, and general cancer.

For most of the behavioral suggestions given by the CIS information specialists, there were no differences between African American and White callers within each of the three major caller groups (i.e., patients, symptomatic callers, and general public). Statistically significant differences occurred with respect to suggestions to call NCI among patients and suggestions to read literature among the general public.

African Americans reported considerable satisfaction with their use of the CIS. They did not report feeling alienated or rudely treated by the information specialists. They did have numerous recommendations on reaching African Americans more effectively. Most of their suggestions called for more targeting to the African American community and more personalization of the messages.

Potential Strategies for Reaching African Americans

Television continues to emerge as an important source of health information for African Americans, regardless of socioeconomic status. Other important sources such as African American magazines, African American radio, and general and African American newspapers may be underused. The less-educated African Americans reported reading newspapers quite frequently. The importance of the credibility of the information was quite clear. In general, African Americans trusted African American media more than White media, but trust was still reasonably high for general media and particularly for specialized information sources such as ACS, NCI, and the CIS. The CIS, when referred to by telephone number, received a lower rating of trust than when referred to by name. Perhaps there is a problem with the perception of the telephone as a means of information seeking. The qualitative research provided more evidence of the credibility problem. Spokespersons must be chosen carefully. There seemed to be a preference for ordinary African American people who had experienced and overcome a problem.

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NOTES

¹Because the sample sizes are so large, very small differences between African American and White samples produce statistically significant results using a z test for proportional differences. Rather than discussing all of these statistically significant differences, only the largest differences will be highlighted.

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Cancer Patients' Search for Information

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This study explored the information-seeking behavior of 257 cancer patients or their relatives who received specific, treatment-related information from the Illinois office of the Cancer Information Service (CIS); it also explored the information-seeking behavior of a sample of 262 other cancer patients matched for age, gender, race, cancer site, and type of hospital where first seen. Among the matched patients, 53% sought information from at least one source besides their physicians. These information seekers were similar to the selected CIS patients in many respects. Compared with patients who did not seek information, both CIS patients and these other information seekers were more likely to have felt more stressed when first diagnosed, to have sought a second opinion, to have been seen at more hospitals and by more physicians since diagnosis, to prefer greater information about and involvement in their treatment plans, and to have been less confident that physicians always have the most current cancer knowledge. The majority of both information-seeking groups sought explanatory information about their cancer or treatment, and most wanted information just after their diagnosis and before starting treatment. Those in the comparison sample, however, had less well-defined questions and consulted fewer sources; only a few of them received the type of information provided by the CIS, and they were less likely to discuss with their physicians the information obtained from various sources. [Monogr Natl Cancer Inst 14:93-104, 1993]

INTRODUCTION

Fifty-two percent of the calls received by the Cancer Information Service (CIS) in 1989, excluding calls to the Publications Ordering Service, were from cancer patients and their relatives or friends (CIS call record data from the CIS project officer, Kate Duffy Mazan, National Cancer Institute, Bethesda, Md.). For many of these callers, the CIS served mainly to clarify and reinforce information they already had received from physicians or served as a source of information about coping with the emotional or practical aspects of cancer. Of the approximately 184 000 cancer patients and their families who called the CIS in 1989, however, about 24 000 also received a referral for a consultation or second opinion, and 32 000 received information about clinical trials. More than 17 000 received a printout from a computerized search of Physician Data Query (PDQ), a database containing state-of-the-art treatment options for all types of cancers, a listing of ongoing National Cancer Institute (NCI)-approved clinical trials,

and directories of physicians and hospitals specializing in cancer care (1). Thus, a sizeable subset of CIS callers received information that could affect treatment decisions. Moreover, given the nature of such information, using it would require discussing it with their physicians, thus increasing the chances of its diffusion.

One objective of this research was to determine what information needs led this group of CIS callers to contact the service, whether the information they received was useful for clinical decisions, and/or whether they shared it with their physicians. Although prior user surveys indicate that cancer patients and their relatives who call the CIS tend to be very satisfied with the service (2), little evidence is available on how callers use the information they receive from the CIS. One study that followed up callers who had cancer symptoms but had not yet been diagnosed at the time of the call found that the majority of these callers subsequently contacted a health professional, and about half of those who did attributed this action to having talked with CIS staff (3). The study concluded that the CIS served both an information and a social support function and that both the information and the social support contributed to the callers' subsequent health-related behavior. In the present study, we asked questions about what information was desired from the CIS, whether the information received was shown to or discussed with the patient's physician, and whether the information obtained helped the patient or the physician make decisions about treatment or management.

A second objective of this study was to assess the degree to which the characteristics and information-seeking activities of these selected CIS callers are prevalent among a matched sample of cancer patients in general. For example, how do the information needs of these two groups compare at different stages of the disease? What proportion of the matched cancer patients also seek information and, if they do, from whom? Do either of these groups represent the increasing numbers of patients who want to participate in treatment decisions rather than assume the more traditional role of the passive patient (4)? Several studies have shown that the patient's seeking and processing of information and the patient's involvement affect their response to serious illness. Information seeking helps patients maintain a sense of control in the face of a highly threatening disease (5-8) and cope with uncertainty (9,10). In addition, there is evidence that, compared with a poorly informed patient, a well-informed patient, actively participating in treatment plans, is more likely to adhere to

*See "Notes" section following "References."

treatment regimes (9,11,12), cope with the illness (10,13,14), and recover (7,13). It is unclear, however, whether it is the being informed, per se, that produces these benefits or whether patients who seek information are those who already have better coping skills. It is a goal of this paper to add to the understanding of what leads patients to seek and use information related to their cancer treatment.

A third objective was to explore the outcomes of the patients' information-seeking activity—defined as purposely seeking information about their disease and its treatment from sources other than their treating physicians—including whether they share that information with their physicians. This objective is of particular interest because physicians are likely to be the patients' primary source of information about their disease and its management and because both the patient-initiated search for treatment information and the act of bringing such information to the physician's attention are inconsistent with the traditional patient role (4). Patient-physician communication has been found to be least effective when conducted in a manner inconsistent with the role expectations of both patients and physicians (15,16). Although there is increasing recognition of the benefits of patients' participation in the management of their illness (5,17), such participation is often still perceived as being limited to participation in choosing among alternative courses of action proposed by the physician. Even then it is acknowledged as a departure from traditional roles, a departure that requires tactful negotiating on the part of the patient (18). On the other hand, the request for a second opinion is a well-accepted practice, some health professionals are advocating greater sharing of decisions with patients (19), and patient advocates advise patients to consider all of the choices and resources available before deciding on a given treatment plan (20,21). Seeking treatment-related information from sources such as the CIS and discussing the information with one's physician is consistent with this trend, but patients may still feel uncertain about how to engage in these new patient-physician interactions.

In short, this study had three main objectives. The first was to identify the characteristics and activities of a subset of cancer patients known to have obtained state-of-the-art treatment information or referrals to cancer experts through their information-seeking initiative (i.e., calling the CIS). The second objective was to determine the degree to which similar characteristics and information-seeking activities occur among cancer patients in general and what information sources they consult. The final objective was to determine whether the information obtained by patients in either sample was perceived as useful for making treatment decisions and whether patients discussed the information with their physicians.

METHODOLOGY

Sample Design

Two samples of cancer patients were selected for this study. The first sample included cancer patients or their

relatives who had called the Illinois CIS and who had received specific treatment-related information. The second sample, referred to as the "comparison sample," included cancer patients and was selected from a general population of cancer patients diagnosed or treated at Illinois hospitals. The comparison sample was matched to the CIS sample for selected characteristics of the patient and the hospital of diagnosis or initial treatment.

CIS sample. The CIS sample was selected from among cancer patients and relatives of cancer patients who called the Illinois CIS between October 1988 and October 1989. During this period, qualifying callers were asked for their permission to be recontacted for an interview. Callers qualified if 1) they received from the CIS a physician or hospital referral name, a printout from a PDQ computer search, or information about a clinical trial related to the patient's cancer; 2) they were diagnosed cancer patients or their relatives; 3) the patients had a diagnosed lymphoma (Hodgkin's or non-Hodgkin's) or cancer of the breast, lung, colon, or prostate; and 4) they were 18 years of age or older. During the study period, 702 callers met these criteria. Of these, 477 gave permission to be recontacted, 24 refused permission, and 201 were not asked because the CIS staff were too busy, forgot, or felt the caller was too distraught.

This sample of 477 CIS callers was further screened, just prior to conducting telephone interviews, to exclude patients diagnosed before January 1, 1986, and relatives who were not sufficiently involved in the patients' care to be able to answer the interview questions. Forty-two patients diagnosed before January 1, 1986, were excluded because we felt that patients with long-standing cancers might have different information needs than those with more recent diagnoses. Relatives were interviewed only if they had called on behalf of an eligible cancer patient, if the patient caller had died, or if the patient was too ill to be interviewed *and* if he or she met all of the following criteria: 1) was over 18 years of age, 2) was a close relative of the patient, 3) usually accompanied the patient on doctor visits, and 4) was very involved with the patient's illness and medical care decisions. Eighty-one relatives who did not meet all of these conditions were excluded from the study.

The screening procedures described above yielded 354 eligible patients and relatives. A total of 257 (73%) completed the interview, 34 (10%) refused, and 63 (18%) had died, could not be contacted, or could not be located. Of the 257 completed interviews, 114 were conducted with relatives, most of whom were either spouses (43%) or children (46%) of patients and all were very involved in the patient's illness and medical care decisions. By design, the CIS sample included roughly equal numbers of patients with each of the selected cancers. Interviews were completed for 68 breast, 62 colon, 68 lung, and 59 combined lymphoma or prostate cancer patients.

Comparison sample. The comparison sample was matched to the CIS sample at an aggregate level on several patient and hospital characteristics. The patient characteristics were gender, cancer site, median age by cancer site,

and—to the extent possible—time elapsed since diagnosis. The matching variables for the hospital where the patient was diagnosed or first treated were geographic location (i.e., located in one of the two largest metropolitan statistical areas in Illinois, in any other Illinois metropolitan statistical area, or elsewhere in the state); number of beds (i.e., ≤ 250 , 251–450, > 450); and whether the hospital was affiliated with a medical school and had a cancer program approved by the American College of Surgeons (i.e., affiliated with a medical school and had an approved cancer program, had an approved cancer program only, affiliated with a medical school only, neither).

This sample was identified through the Illinois State Cancer Registry and through tumor registries maintained by Illinois hospitals. A portion of the sample was selected from hospital tumor registries because the time lag for cases to enter the state registry prevented identification of recently diagnosed cases. A two-step procedure was required to obtain permission to select and contact sample patients: first hospitals and then the sampled patients' physicians had to agree to participate. A total of 111 Illinois hospitals were contacted and 64 (58%) agreed to participate, 29 (26%) refused, and 18 (16%) were noncontacts or were unable to complete the approval process within the required time period. Of the 64 hospitals that were willing to participate, 55 were able to provide matching cases. Of the 365 physicians who were contacted, 249 (68%) gave permission to contact the patients, and 116 (32%) did not. Of the 521 identified patients, 306 (59%) were eligible, 99 (19%) were ineligible, and 116 (22%) patients were those for whom the 116 physicians refused permission to contact. Interviews were completed with 262 respondents (86%), 26 (8%) refused, and 18 (6%) were noncontacts or unlocatable. Most of the 262 interviews were conducted with patients; only 24 (9%) were conducted with relatives who met the same criteria as those required for the CIS sample.

Preliminary analysis indicated that the comparison sample comprised two distinct subgroups based on whether or not the patient sought information from sources other than his or her physicians. Therefore, study results are presented for each of the following three groups:

- Cancer patients or relatives in the selected CIS sample (termed "CIS Info-Seekers," $n = 257$).
- Comparison-sample cancer patients or relatives who sought information from at least one source besides their treating physicians ("Other Info-Seekers," $n = 138$).
- Comparison-sample patients or relatives who did not seek information other than from their treating physicians ("Non-Seekers," $n = 124$).

Comparability and generalizability of samples. Overall, the CIS and comparison samples were successfully matched on patients' gender, cancer site, and median age by cancer site and on all of the hospital characteristics. There were no significant ($P \leq .01$) differences between the two samples on any of these variables. Three sampling issues need to be kept in mind when interpreting the study findings, however.

First, procedures used to accrue the two samples "screened out" a number of potential subjects (i.e., CIS staff did not ask 29% of potentially qualifying callers for permission to recontact them and physicians denied permission to contact 22% of potentially qualifying comparison patients). Both CIS staff and physicians may have excluded the more distraught or more ill patients, thus diminishing generalizability of the study findings to this type of patient. This loss, however, was of similar magnitude in both samples. Among the eligible cases, completion rates were similar in the two samples and within acceptable ranges for patient surveys.

Second, the CIS and comparison samples differ on time elapsed between diagnosis and interview. Time since diagnosis was significantly longer for the comparison sample because of the time required for patients to be entered in registries and for obtaining permission from hospitals and physicians to contact sampled patients. Being interviewed closer to diagnosis should not affect recollection of the patient's initial response to his or her cancer diagnosis, treatment, and sources consulted for information on which the questionnaire items focused. These topics are salient to the respondent and not likely to be forgotten. Time since diagnosis, however, is controlled for in the data analysis.

Third, the samples differ in the proportion of respondents who were relatives of cancer patients. Relatives represent a large portion of CIS calls for cancer patients. To exclude them from this study would have resulted in an incomplete picture of the information-seeking patterns of these patients, which includes help from relatives. In the comparison sample, the accrual procedures led to explicit identification of a relative as the spokesperson for the patient in only 9% of the cases. Attempts to identify relatives who might have helped the remaining comparison patients would have added considerably to the already onerous effort to identify the matched sample. Moreover, other bias would have been introduced, such as patients' ability to identify the appropriate relative, additional attrition due to the need to obtain referral to and cooperation from this new individual, and the awkwardness of asking this third party (not identified through his or her own actions, as is the case for the relatives in the CIS sample) for information about the cancer patient whom we needed to contact in the first place. Upon further analysis, CIS patients and their relatives were found to differ only on characteristics unlikely to alter the study findings. These characteristics are discussed later in this report.

Data Collection and Analysis

The questionnaire used was essentially the same for both relatives and patients in both the CIS and comparison samples. Interviews were conducted by telephone and averaged 33 minutes in length. All interviews were conducted by professional interviewers hired and trained specifically for this study.

Variables examined in this research include patient demographics, illness, and source of care characteristics;

patient satisfaction with the extent to which physicians explained and answered questions about their diagnosis and treatment; attitudes toward physician-patient dialog; and information-seeking activities and use of information. Demographic characteristics of patients included gender, age, and education. The illness variables were cancer site and degree of stress when first informed of the cancer diagnosis (rated on a scale of 1 to 10). The source of care variables included specialty of physician at first diagnosis, numbers of physicians and hospitals seen since diagnosis, and whether the patient sought a second opinion.

Four variables were related to patient satisfaction with the physician's explanation of the diagnosis and treatment. For each physician seen since diagnosis, respondents were asked whether the physician explained or discussed the diagnosis and treatment and whether they asked the physician any questions about diagnosis or treatment. If the patient had asked questions of a physician, we asked how comfortable they felt doing so and how clear the physician's answers were. For each of these variables, a single average value was calculated for all of the physicians seen by each patient.

Patients' attitudes toward physician-patient dialog were measured by use of a series of 14 questions which included questions about their involvement in treatment decisions. A factor analysis of the 14 variables indicated that three conceptual variables should be created from these data (22). Five of the variables have high, consistent loadings ranging from 0.62 to 0.74 on a factor we label "prefer involvement." This factor reflects patients' preferences for physicians' sharing of information and decisions with them. Four of the variables have loadings ranging from 0.57 to 0.90 on a factor we call "information needs." This factor reflects patients' desire for and ability to understand information from physicians. Finally, two of the variables loaded at 0.80 on a third factor we call "trust physicians have current knowledge." This factor reflects patients' levels of confidence that physicians have current knowledge before making diagnoses or developing treatment plans. Three composite variables were created by averaging the question values for each respondent on the variables that reflect each factor. The Cronbach's Alpha reliabilities for the three composite variables are 0.68, 0.73, and 0.44 respectively.¹

The final group of variables is related to information-seeking activities and use of information. All respondents were asked if they sought information from each of the following sources: the CIS; the American Cancer Society; NCI; a hospital or cancer center; a patient support group; any other organization; literature such as a book, journal, or pamphlet; relatives or friends; or any other source. Respondents in the comparison sample were asked whether during the diagnosis or treatment period of their illness they were aware of the NCI telephone information service and, if aware, if they had ever called the service. Information-seeking activities related to each source the patient had consulted were explored with queries about the time during their illness when the source was consulted

(just after diagnosis, while in treatment, after treatment), the type of information sought, satisfaction with the information, whether it had been helpful for treatment decisions, how the information was useful, and whether it was mentioned to the patient's physicians.

Results are presented as percentage distributions or means for continuous variables for each group. Across-group comparisons were performed with cross tabulation χ^2 tests of significance for nominal and ordinal variables. Analyses of variance (ANOVAs) were computed for interval variables, and significance was determined by an F test. Scheffe multiple comparison tests were used in the ANOVA procedures to determine which group differed significantly. Significance tests are reported at $P \leq .05$.

RESULTS

A number of patterns emerge when we examine the patient demographic and illness characteristics data in Table 1. Although the overall comparison sample was matched to the CIS sample for gender and age, the Non-Seekers are more likely to be male, to be over age 60, and to have no college education than either the CIS Info-Seekers or the Other Info-Seekers. There were, however, no differences among groups on cancer site or on presence of a second or metastatic cancer.

Differences exist between patients who sought information and those who did not concerning self-reported amounts of disease-related stress and social support. Both CIS Info-Seekers and Other Info-Seekers, compared with Non-Seekers, are more likely to have greater stress associated with their cancer diagnosis (means of 7.43 and 6.60 versus 5.27), to talk a lot with others about their cancer (70% and 49% versus 30%), and to have somebody who helped them to cope emotionally (76% and 62% versus 42%).

Having or not having sought information is not affected by type of hospital or physician with whom the patient was first in contact. Although matching procedures explain the CIS and the overall comparison samples' similarity on type and size of the hospital at first diagnosis or treatment, there are also no differences in these variables between the two comparison subgroups, and there are no differences between the three groups in specialties of physicians who first diagnosed the disease.

After diagnosis, patients who sought information are more likely than Non-Seekers to have seen more physicians and visited more hospitals. The proportions who saw four or more physicians since diagnosis are 54% for CIS Info-Seekers, 40% for Other Info-Seekers, and 20% for Non-Seekers. The proportions seen at more than one hospital are 50%, 44%, and 24%, respectively. Similarly, 62% of CIS Info-Seekers, 53% of Other Info-Seekers, and 37% of Non-Seekers sought a second opinion.

Table 1. Patient characteristics, by study groups

Patient characteristic	Study group, %			χ^2 , F test, or Scheffe	df
	CIS Info-Seekers (n = 257)	Other Info-Seekers (n = 138)	Non-Seekers (n = 124)		
<i>Patient demographic and illness characteristics</i>					
Gender					
Male	40	32	52	10.16*	2
Female	60	68	48		
Age, y					
< 50	26	28	11	28.12†	6
50-59	28	35	24		
60-69	30	25	34		
> 69	17	12	30		
Education					
Some high school	14	18	34	32.36†	6
High-school graduate	33	38	36		
Some college	24	25	19		
College graduate	29	20	11		
Cancer site					
Colon	24	22	29	NS‡	
Breast	27	33	23		
Lung	26	20	28		
Lymphoma or prostate	23	25	20		
Level of stress at diagnosis					
Low (1-3)	14	24	39	21.14† a,b,c§	2
Medium (4-7)	24	23	34		
High (8-10)	62	53	27		
Mean	7.43	6.60	5.27		
Standard deviation	2.9	3.2	3.1		
<i>Social support</i>					
Talked a lot to others about their cancer					
Yes	70	49	30	58.73†	2
No	30	51	70		
Somebody helped patient to cope emotionally					
Yes	76	65	42	43.03†	2
No	24	35	58		
Somebody usually accompanied patient on doctor visits					
Yes	69	72	60	NS	
No	31	28	40		
<i>Sources of care at diagnosis</i>					
Hospital bed size					
< 250 beds	20	22	28	NS	
251-450 beds	38	41	38		
> 450 beds	42	37	34		
Hospital type					
Medical school and cancer program	57	59	57	NS	
Medical school only	3	2	2		
Cancer program only	25	25	29		
Neither	15	14	12		
Specialty of physician who first made or communicated diagnosis to patient					
Primary care	35	33	34	NS	
Oncology	15	16	10		
General surgeon	22	26	31		
Other	28	25	25		

Table 1. Patient characteristics, by study groups—Continued

Patient characteristic	Study group, %			χ^2 , F test, or Scheffe	df
	CIS Info-Seekers (n = 257)	Other Info-Seekers (n = 138)	Non-Seekers (n = 124)		
<i>Contact with care since diagnosis</i>					
Number of physicians seen					
1 or 2	22	35	53	55.07†	6
3	24	25	27		
4	23	25	14		
5-13	31	15	6		
Number of hospitals					
1	50	56	76	41.32†	4
2	30	38	22		
3 or more	20	6	2		
Patient sought a second opinion					
Yes	62	53	37	21.36†	2
No	38	47	63		
Time between diagnosis and date of interview					
≤2 mo	35	0	0	155.30†	6
3-4 mo	19	7	7		
5-11 mo	20	63	56		
≥ 12 mo	26	30	36		
<i>Communication experience with treating physicians</i>					
Physician(s) explained diagnosis and treatment (no = 1, yes = 2)					
Mean across physicians	1.87	1.86	1.84	NS	
Standard deviation	0.24	0.23	0.24		
Patient asked questions of physician(s) (no = 1, yes = 2)					
Mean across physicians	1.86	1.75	1.59	31.26† a,b,c§	2
Standard deviation	0.26	0.31	0.36		
Comfortable asking questions of physician (very uncomfortable = 1, very comfort- able = 4)					
Mean across physicians	3.40	3.54	3.55	3.86 d§	2
Standard deviation	0.56	0.54	0.54		
Clarity of physician's answers (very unclear = 1, very clear = 4)					
Mean across physicians	3.40	3.52	3.43	NS	
Standard deviation	0.55	0.49	0.53		
"Prefer involvement" attitude (prefer little involvement = 1, prefer strong involve- ment = 4)					
Mean	3.50	3.30	3.08	56.88† a,b,c§	2
Standard deviation	0.37	0.35	0.35		
"Information needs" attitude (low informa- tion needs = 1, high information needs = 4)					
Mean	2.71	2.07	1.78	115.13† a,b,c§	2
Standard deviation	0.60	0.62	0.60		
"Concern that physicians have current knowledge" attitude (low concern = 1, high concern = 4)					
Mean	2.54	2.36	2.28	9.37† a,b§	2
Standard deviation	0.61	0.56	0.46		

Table 1. Patient characteristics, by study groups—Continued

Patient characteristic	Study group, %			χ^2 , F test, or Scheffe	df
	CIS Info-Seekers (n = 257)	Other Info-Seekers (n = 138)	Non-Seekers (n = 124)		
Still have unanswered questions					
Yes	40	14	9	56.35†	2
No	60	86	91		

*Significant at $P \leq .01$.

†Significant at $P \leq .001$.

‡NS = not significant.

§F test and Scheffe multiple comparisons were done on all continuous variables. a = CIS Info-Seekers and Other Info-Seekers are significantly different; b = CIS Info-Seekers and Non-Seekers are significantly different; c = the comparison groups are significantly different from each other; d = no two groups are significantly different.

||Significant at $P \leq .05$.

The three groups are equal in stating that their physicians explained the diagnosis and treatment to them and in rating the physicians' answers to their questions as clear or very clear. Both information-seeking groups (CIS Info-Seekers, Other Info-Seekers) are more likely to have asked questions of their physicians than the Non-Seekers (means of 1.86, 1.75, and 1.59). The CIS Info-Seekers show a slightly lower mean on whether they were comfortable or very comfortable asking questions of their physicians.

Those who sought information feel strongly that patients should be informed and involved in decisions about their care. Mean scores for the composite variable "patient involvement" are 3.50 for CIS Info-Seekers, 3.30 for Other Info-Seekers, and 3.08 for Non-Seekers. For the composite variable "information needs," mean scores are 2.71, 2.07, and 1.78, respectively. The CIS Info-Seekers are less likely, followed by Other Info-Seekers, to trust that physicians make sure they have current knowledge before making diagnoses or treatment decisions. Their mean scores on this variable are 2.54 and 2.37 compared with 2.27 for Non-Seekers.

For most of the statistically significant comparisons in Table 1, there is a hierarchical pattern of CIS Info-Seekers being the most likely to have the characteristic, the Other Info-Seekers being next, and the Non-Seekers being the least likely to have the characteristic. Interestingly, 40% of CIS Info-Seekers, versus 14% of Other Info-Seekers and 9% of Non-Seekers, still have unanswered questions about their cancer. It is likely that many CIS Info-Seekers still have questions because they are close to their diagnosis and, thus, may not yet have all of the information they need and because, as indicated above, they have higher information needs than other patients. Finally, 55% of the patients in the comparison sample were aware of the CIS, including 64% of the Other Info-Seekers (10 of whom called the CIS) and 43% of the Non-Seekers.

As expected, the CIS and the comparison samples differ in time since diagnosis and in the proportion of respondents who were relatives rather than cancer patients. In addition, the comparison patients were not matched on educational level, a personal fact that could be identified only upon interview. The comparisons presented in Table

1 were repeated, controlling for each of these three variables. When the relationships in Table 1 were reexamined, controlling for education, all previously significant relationships remained significant except for age. To explore the effect of time elapsed since diagnosis, we first repeated the analysis, excluding the 35% of the CIS Info-Seekers interviewed within 2 months of diagnosis. All the findings reported above for Table 1 remained unchanged. Second, we repeated all comparisons among the three study groups, controlling for number of months since diagnosis. The results remained unchanged, except that the initial group differences in concern that physicians have current knowledge were no longer significant. More than 40 comparisons were made when we controlled for time since diagnosis. In making this many comparisons, it is not surprising that one difference was found, and this could be due simply to chance. Also, a longer elapsed time since diagnosis could have increased the opportunity for more health care contacts or information-seeking activities among the comparison patients, but the findings are in the opposite direction.

To explore differences by type of respondent, we compared the CIS patients with the CIS relatives on all the variables in Table 1. Compared with cancer patients who themselves called the CIS, cancer patients for whom a relative called are older (57% versus 38% are 60 years or older), less educated (22% versus 8% have less than high-school education and 23% versus 34% are college graduates), more likely to be male (50% versus 31%), more likely to have lung cancer (35% versus 20%), and less likely to have breast cancer (11% versus 38%). In addition, patients for whom a relative called were more stressed by their diagnosis and were more likely to have someone usually accompany them on physician visits. All the remaining characteristics were the same whether patients or relatives made the CIS call. Thus, the differences reported above between the CIS Info-Seekers and the two other groups would not change if including only the CIS patients or controlling for type of respondent. This analysis does not address a more important issue: Could the

comparison patients also have relatives acting in their behalf who, if we had identified and interviewed them, would have changed the findings for these patients? The nature of many of the questions and the trend of the overall findings suggest that this is not the case. Many of the items on which Non-Seekers differ from both CIS and Other Info-Seekers are factual information items—such as number of doctors seen, number of hospitals visited, and receiving a second opinion—that are unlikely to change by type of respondent. Second, the Non-Seekers tend not to have talked a lot with others about their cancer and not to have someone who helped them cope emotionally, suggesting that these individuals are less likely to enlist others to help them deal with the disease.

In short, our results do not change dramatically when controlling for three variables on which matching was not possible: education level, time elapsed between diagnosis and interview, and whether the respondent was a patient or a relative. Four items for which CIS patients and relatives differ considerably (age, gender, education, cancer sites) simply indicate the type of patient for whom a relative is more likely to call the CIS.

The remaining comparisons are between CIS Info-Seekers and Other Info-Seekers. The 124 comparison patients who did not seek any information could not be queried about the process of seeking information and are, therefore, excluded from the remaining analysis. As shown in Table 2, CIS Info-Seekers (54%) are more likely than Other Info-Seekers (40%) to have sought information from two or more sources (not counting the CIS). The sources consulted, excluding the CIS, are similar across groups, however. Seventy-three percent of CIS Info-Seekers and 74% of Other Info-Seekers consulted printed information. Relatives and friends are the next most common source, consulted by 40% and 46% of the patients, respectively. No more than 12% in either group

consulted patient support groups, the American Cancer Society, other organizations, or hospitals or cancer centers. Only 7% of Other Info-Seekers contacted the CIS.

Table 3 shows the proportion of patients who consulted each of these sources at different times during their illness. Patients in both groups were most likely to seek information just after diagnosis and before starting treatment—77% of CIS Info-Seekers and 74% of Other Info-Seekers. The proportions seeking information from printed materials and family and friends are quite similar in the two groups and at any of the four indicated times relative to the illness.

Patients were asked what information they wanted from each source they consulted. Responses were coded into the six main categories listed in Table 4. The category “explanatory, treatment” includes questions such as “What will be done to me as part of such and such surgery or therapy?” or “Why am I given this type of medication?” The “treatment options” category includes questions such as “What is the best treatment for someone with my type of cancer?” That is, patients coded in the “explanatory . . .” categories are primarily interested in a better understanding of their treatment, whereas patients in the “treatment options” category are primarily interested in learning what treatment options are available to them.

Table 4 shows that, with the exception of the CIS interaction, patients in the two groups are very similar in their information needs and the sources they consulted. This similarity is particularly noteworthy due to the fact that the CIS respondents were selected because they received specific information. The majority of patients in both groups are most likely to seek explanatory information about their cancer or about their treatment. This information was sought from at least one source by 87% of CIS Info-Seekers. Among Other Info-Seekers, 73% sought explanatory information about their cancer and 67% about treatment. The next most commonly sought type of infor-

Table 2. Number and type of sources consulted, by CIS Info-Seekers and Other Info-Seekers

	Study group, %		χ^2	df
	CIS Info-Seekers (n = 257)	Other Info-Seekers (n = 138)		
Number of sources consulted (including the CIS, excluding treating physicians)				
1	46*	60	12.62†	2
2	38‡	35		
3 or 4	16‡	5		
Type of sources consulted				
CIS	100	7		
Printed materials	73	74		
Relatives, friends	40	46		
Patient support groups	12	10		
American Cancer Society	11	9		
Other organizations	11	4		
Hospitals or cancer centers	6	0		

*Either the CIS only or the CIS and one other source.

†Significant at $P \leq .01$.

‡In addition to the CIS.

Table 3. When and from whom information was sought, by CIS Info-Seekers and Other Info-Seekers*

Information source	Just after diagnosis		While in treatment		Between treatments		After treatment	
	CIS	Other	CIS	Other	CIS	Other	CIS	Other
CIS	49	5	31	1	27	1	15	1
Printed material	51	48	27	24	27	24	16	20
Family and friends	37	37	20	21	16	21	8	5
Any source (excluding physicians)	77	74	59	49	46	33	28	24

*n = 257 for CIS Info-Seekers; n = 138 for Other Info-Seekers. Values = %.

mation, about coping and support, was sought by 65% of patients in each group. These three types of information were sought more often from physicians than from any other source.

Although all CIS Info-Seekers had, by sampling criteria, received at least one of the following information items, the proportions of CIS Info-Seekers who wanted that information from any source were 60% for treatment options, 29% for clinical trials, and 28% for referrals. Among Other Info-Seekers the proportions were 38% for treatment options, 7% for clinical trials, and 7% for referrals. It is interesting to note, however, that CIS Info-Seekers were as unlikely as Other Info-Seekers to seek information about clinical trials or referrals from their physicians or any other source besides the CIS. For this type of information, the CIS was the preferred source. Finally, regardless of the many similarities in the information needs of the two groups, very few of the patients in the comparison sample obtained the type of information received by those who called the CIS. Among Other Info-Seekers, seven (5%) obtained a PDQ printout, three of whom also called the CIS; 21 (15%) obtained a referral; and 7 (5%) obtained clinical trials information (data not presented in Table 4.)

Most respondents (between 80% and 90%) felt that the information received from the CIS or from each of the other sources had been useful or very useful. Of more interest are the patients' perceptions that the information was helpful for treatment decisions, how it was helpful, and whether it was discussed with their physicians (Table 5). Usefulness for treatment decisions was determined by the question: "Did the information obtained from [the

CIS' or 'any of these other people and places which you have contacted'] help to make decisions about your treatment or care?" Thirty-eight percent of CIS Info-Seekers answered yes to this question about CIS information. Of these, 67% stated that the information made them feel more knowledgeable, more able to understand and discuss with the physicians the options available to them, and more confident of having explored all options and chosen the best one. An even more direct impact on treatment decisions was suggested by the 12% who reported that the CIS information helped them to find a new physician or led them to seek a second opinion and by the 10% for whom the information helped to decide for or against a specific treatment.

Forty-two percent of CIS Info-Seekers discussed information received from the CIS with their physicians. The specificity of the information received by these patients allowed further determination of how it was used. Eighteen percent of the 195 patients who remembered having received a referral or names of physicians or institutions associated with clinical trials made contact with them. Of the 159 patients who remembered the PDQ printout, 27% discussed the printout with or showed it to their physicians. Fifty-one percent took at least one of these three actions.

Thirty-two percent of CIS Info-Seekers and 27% of Other Info-Seekers felt that information from all other sources (excluding physicians) had been useful for treatment decisions, and the ways in which usefulness was described are similar to those reported for the CIS information. CIS Info-Seekers, however, were significantly more likely to discuss with their physicians information they obtained from other sources: 53% of CIS Info-

Table 4. Type of information wanted from sources consulted, by CIS Info-Seekers and Other Info-Seekers*

Type of information sought	Physicians		CIS		Literature		Family/friends		Organizations		Any source†	
	CIS	Other	CIS	Other	CIS	Other	CIS	Other	CIS	Other	CIS	Other
Explanatory, cancer	63	51	46	2	49	44	7	9	14	4	87	73‡
Explanatory, treatment	53	56	23	1	18	15	5	0	5	4	86	67‡
Treatment options	39	28	21	1	18	12	5	4	4	1	60	38‡
Clinical trials	4	1	23	1	8	3	0	1	5	0	29	7‡
Referrals	6	4	16	0	2	0	6	3	4	1	28	7‡
Coping, maintenance	37	38	12	0	18	20	21	27	13	11	65	65

*n = 257 for CIS Info-Seekers; N = 138 for Other Info-Seekers. Values = %.

†Includes physicians.

‡Significant at $P \leq .001$.

Table 5. Uses of information obtained from the CIS and other sources*

Information use	Information from CIS	Information from all other sources	
	CIS Info-Seekers	CIS Info-Seekers	Other Info-Seekers
Information was helpful for clinical decisions			
Yes	38	32	27
No or don't know	62	64	71
	(n = 257)	(n = 225)†	(n = 138)
How information was helpful			
Felt more knowledgeable discussing options	44	37	40
Was reassured of having made best decision	23	13	16
Found a physician	12	10	14
Changed/decided on treatment	10	13	27
Other reasons	18	33	22
	(n = 98)‡	(n = 70)‡	(n = 37)‡
Patient discussed information with treating physician(s)			
Yes	42	53	37§
No	58	47	63
	(n = 195)	(n = 225)	(n = 138)
Patient contacted a referral or other cancer expert whose name was received from the CIS			
Yes	18	NA	NA
No	82		
	(n = 195)		
Patient showed or discussed PDQ printout with physician			
Yes	27	NA	NA
No	73		
	(n = 159)¶		
Patient took at least one of the three actions listed immediately above			
Yes	51	NA	NA
No	49		
	(n = 195)		

*Unless otherwise noted, values = %. NA = not applicable.

†Includes only CIS Info-Seekers who consulted at least one other source besides CIS.

‡Includes only respondents who answered "yes" to the prior question.

§Proportion of CIS Info-Seekers and Other Info-Seekers who discussed information from any source with their physicians are significantly different at $P \leq .01$.

||Includes only respondents who remembered receiving from CIS at least one of the following: PDQ printout, experimental treatment information, or referrals.

¶Includes only respondents who remembered receiving a PDQ printout.

Seekers did so, compared with only 37% of Other Info-Seekers.

In summary, Other Info-Seekers were as likely as CIS Info-Seekers to consult literature or relatives and friends, seek information just after diagnosis, want information that would help them better understand their disease and treatment, and consider the information they received useful and helpful in making clinical decisions. Compared with CIS Info-Seekers, Other Info-Seekers consulted fewer sources, were less likely to call while in treatment or between treatments, and were less likely to discuss the information they obtained with their physicians.

DISCUSSION

This research was designed to explore three objectives regarding the information-seeking behavior of cancer patients. First, we wanted to know what prompts cancer patients to obtain specific treatment-related information such as PDQ, clinical trials, and referral information from the CIS and at what point in their disease they seek this information. Our data indicate that the call to the CIS is part of intense information-seeking activities that resemble what other authors describe as a way of maintaining mastery in the face of the disease (3,5). These CIS callers

ask for and receive explanations of their diagnoses and treatment from their physicians, seek second opinions, talk a lot with others about their cancers, and seek information from several sources. They tend to be recently diagnosed and to report high levels of stress when first diagnosed. At the same time, these patients are well educated and are sophisticated searchers and users of information. They want to make sure they obtain and understand the most current information about their cancers and many of them discuss the information they obtain with their physicians. The implications for CIS counselors are that they must have skills to meet the needs of patients with high anxiety levels, they must have access to the most current cancer knowledge, and they must be able to communicate this type of information clearly. The high level of satisfaction with the CIS reported by most callers in this study suggests that CIS staff are meeting these requirements.

Second, we wanted to know how similar or different were the information needs and activities of these selected CIS callers and those of cancer patients in general. In the comparison sample, about half of the patients sought information from one or more sources besides their physicians, and half did not. Clearly, there is a sizeable number of cancer patients who do not feel a need for information beyond what they receive from their health-care providers. This finding is consistent with other research indicating that a portion of cancer patients have little desire to participate in their cancer-care decisions (6). Patients in both samples who sought information were demographically similar, and those who did not seek information were more likely to be male, older, and less educated. Compared with patients who seek information, patients who do not are less stressed when first diagnosed; tend to discuss their illness less with others and not to have people who help them cope emotionally; are less likely, after diagnosis, to seek a second opinion; and are more likely to be seen at fewer hospitals and by fewer physicians. Although they are just as likely to have physicians who explain their disease and treatment to them and to find such explanations very clear, they are less likely to ask questions of the physicians, less likely to want to be involved in treatment decisions, and less concerned about whether their physicians have current knowledge.

The information-seeking patients in the comparison sample were similar to the selected CIS callers in many respects. The majority of patients in both groups sought explanatory information about their cancer or treatment, and approximately equal proportions sought information about coping and maintenance. In both groups, most patients wanted information just after their diagnoses and before starting treatment. Overall, however, the information-seeking callers in the comparison sample appear to have weaker and fewer well-defined information needs than the selected CIS callers. They wanted information for the same reasons as CIS callers: to understand their disease better and to feel knowledgeable when discussing treatment options with their physicians. They were, however, unlikely to ask questions or receive information

about clinical trials or referrals, and they consulted primarily printed materials and family and friends. It is unlikely that these sources provide the same type of cancer information provided by the CIS.

We also examined the extent to which treatment-related information is shared with physicians and whether it affects treatment decisions. In contrast to the literature that indicates frequent patient dissatisfaction with physician communication, most of the patients interviewed in this study appeared satisfied with their physicians' communication. Most reported asking for and receiving an explanation of their diagnosis and treatment and felt that their physicians' answers were clear. Patients who sought information from sources besides their physicians also had a strong preference for receiving as much information as possible from their physicians and for being involved in and sharing responsibility for decisions about their treatment. Overall, most patients reported patient-physician interactions that appear conducive to an open discussion of information brought in by the patient. CIS Info-Seekers, however, were more likely than other patients to discuss with their physicians information they obtained from other sources. About half of the patients who called the CIS and over one third of Other Info-Seekers reported doing so.

In addition, data from the CIS sample suggest a potential impact of CIS information on clinical decisions. Because of the nature of the information received by the selected CIS callers, they could be asked specifically whether they discussed the PDQ printout or other CIS information with their physicians and whether they or their physicians contacted a referral obtained from the CIS. Overall, 51% of these CIS callers discussed PDQ or other CIS information with their physicians and/or contacted new physicians. About 19% of the patients reported that the physician asked for more information or consulted another physician or other source about the information (22). Although this is a small proportion (7%) of the overall sample, it indicates that there is a significant potential for CIS-to-patient-to-physician transfer of information. This transfer is more likely to be accepted by physicians if they understand why the patient has become a channel of information. Our findings indicate that a significant proportion of patients wish to be involved in decisions about their care, and they want to be reassured that they have evaluated all their options.

Finally, future research should consider issues not addressed in this study. First, our inference that CIS information is transferred by patients to physicians is based on patients' perceptions. More research is needed to test the hypothesis that such transfer occurs and that it affects clinical decisions. Second, our data did not address how stage and extent of disease may have affected information seeking and use. These are important dimensions that need to be further explored but are items for which patients are not the most accurate respondents. Third, our study was limited to five cancer sites. Although these sites include the three most prevalent cancers, other sites need to be examined. Fourth, most patients in this study were

White. Future studies need to explore and identify the information needs of minority populations. Finally, the high proportion of relatives among the CIS callers indicates a need to study the role of the patient's social support network in seeking and using information and on making treatment decisions. This is especially important for male cancer patients, who are less likely than female patients to call the CIS themselves or to seek information from other sources.

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NOTES

¹Further descriptions of these procedures and a list of the 14 items used to construct these variables are available in reference 22.

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Randomized Telephone Smoking-Intervention Trial Initially Directed at Blue-Collar Workers

Beti Thompson, Susan Kinne, Frances Marcus Lewis, Jean A. Wooldridge*

Although smoking prevalence in the United States has declined markedly in recent years, prevalence among blue-collar workers remains high and few successful methods of reaching this group have been identified. The present study was designed to test the relative efficacy of two different approaches to telephone smoking-cessation counseling for blue-collar workers. Our study built on the experience of the National Cancer Institute's Cancer Information Service (CIS) and compared the past CIS smoking-cessation counseling procedure and a modified version of the present procedure. In our trial, callers to a special telephone hotline who asked for information on smoking cessation were randomly assigned to receive counseling under one of two protocols: 1) the past CIS procedure, in which general information was given and cessation materials were sent to the callers, and 2) a version of the present CIS stage-model procedure, adapted by us for use with blue-collar workers, in which callers were given counseling specific to their stage in the smoking-cessation process. The general-information group contained 185 subjects; the stage-model group contained 197. Despite extensive efforts in the present study, it was not possible to recruit the number of blue-collar workers planned for our statistical analysis. Consequently, of a total of 382 subjects recruited, 93 (24.3%) were blue-collar workers, 181 (47.4%) were white-collar workers, and 108 (28.3%) were retired persons who worked part time, student workers, or the unemployed. Our results show no statistically significant differences in either short-term or long-term nonsmoking rates between the general-information group and the stage-model group. In addition, there were no statistically significant differences between the two groups in movement through the stages of cessation. The 6-month nonsmoking rate overall was 19.4%, and the 6-month nonsmoking rate for blue-collar subjects was 16.7%—rates higher than those reported in other minimal-assistance studies of the general population. Given the results of this study, further research is needed to address both recruitment techniques required to reach blue-collar workers who smoke and cessation needs of that subpopulation. [Monogr Natl Cancer Inst 14:105-112, 1993]

The overall prevalence of smoking in the United States is steadily decreasing (1). Unfortunately, some groups of smokers are not giving up the habit as rapidly as are others (1). In recent years, smoking-cessation researchers have focused on such groups and have developed a variety of

materials and techniques to reach these smokers (1). Blue-collar workers are one group in which smoking prevalence remains high. Although prevalence among the entire U.S. population has decreased from 40.4% in 1965 to 29.1% in 1987, prevalence in 1987 among blue-collar workers was estimated at 40.3% for men and 35.4% for women, or 37.2% total (1-3).

Few successful methods for reaching blue-collar workers who smoke have been identified (4). These smokers have not used formal smoking-cessation programs (5) nor have they enlisted in great numbers in work site smoking-cessation activities (5,6). One hypothesis explains their low levels of participation in programs by suggesting that theirs is a subculture in which smoking is a normative behavior and, thus, there is little support for nonsmoking (7,8). This lack of support may make it more difficult for blue-collar workers to enlist in programs where their peers are likely to witness a cessation effort.

Telephone counseling is a simple, anonymous, unobtrusive method of providing minimal assistance to those seeking help with smoking cessation. Telephone counseling for smoking cessation is not uncommon; for example, the Cancer Information Service (CIS) of the National Cancer Institute's (NCI's) Cancer Communications System has responded to numerous smoking-related calls. Minimal-assistance smoking-cessation programs in general have been shown to be efficacious (9), but the effectiveness of telephone hotlines in smoking-cessation counseling remains somewhat equivocal. Two early studies (10,11) indicated that such services were poorly utilized when offered as adjuncts to smoking-cessation programs. Another early study (12), however, found that users of a telephone hotline had twice the maintained quit rate of nonusers. When telephone assistance is promoted with ongoing media campaigns, use of the service remains high (13). Finally, there is some evidence that brief telephone counseling in conjunction with self-help materials will increase cessation rates (14).

Little is known about whether some telephone counseling protocols in general and in our target population in particular are more effective than others. In this paper, we report the results of a randomized trial of two different telephone counseling protocols for smoking cessation initially targeted to blue-collar workers who smoke.

*See "Notes" section following "References."

BACKGROUND

Telephone Smoking-Cessation Counseling

This study builds on the experience of the existing CIS national network. NCI operates the CIS, a toll-free telephone information and referral resource based in 22 local offices around the United States. Initially, the CIS telephone counselors provided general information about smoking cessation and sent descriptive materials such as pamphlets and fliers to callers who asked for assistance in smoking cessation. The specific content of this approach was eclectic and somewhat dependent on the individual CIS office. This initial approach, called the general-information approach, constituted one arm of our study. In 1987, the CIS adopted a different protocol for counseling smokers.

The new telephone smoking-cessation protocol, based on the stage model of Prochaska and DiClemente (15,16), provided the following for counselors' use: 1) information on expected general areas of callers' questions within the stage model of smoking cessation; 2) appropriate stage-model responses to callers' questions within those areas; 3) fact sheets concerning smoking, smoking and cancer, and smoking-cessation problems; and 4) sample scenarios that might be encountered. The new stage-model approach made up the second arm of our study. This model of telephone counseling had never been tested against the previous CIS model of providing general information; therefore, it was not known whether this approach was more likely to increase cessation rates.

General-Information Intervention

Under the general-information approach, telephone counselors in our study, using general-information sheets on smoking, responded to callers' specific questions about smoking cessation. Counselors did not offer unsolicited advice and messages but merely responded to the callers' questions. A number of fact sheets were available to the counselor in which appropriate responses to general questions were listed. Conforming to the example, a caller asking about avoiding weight gain during smoking cessation would be advised to chew sugarless gum and eat healthy snacks; a caller asking about the benefits of quitting would be given information on health and financial benefits. As a follow-up, callers were sent general materials on smoking cessation after their conversations with the telephone counselor. In short, this group was provided the kind of information that is generic and easily available to any smoker in this society.

Stage-Model Intervention

The stage-model approach is based on the recognition that smoking cessation is a process, not a discrete event. Smokers fall into at least five categories in this model: precontemplators, who are not even thinking of quitting; contemplators, who are thinking of quitting sometime in the near future; action quitters, who have set a quit date

or made an initial quit attempt; maintainers, who have successfully remained smoke free for an extended period; and relapsers, who were initially successful in quitting but are currently vulnerable to resuming the habit (15,16). This model has been extensively tested (17), and increasingly, materials for cessation are being developed around it.

In this arm of the study, callers seeking information on quitting smoking were given messages appropriate to their stage in the cessation process. After their stage was identified, callers were encouraged to move along the cessation continuum. Callers, for example, who said that they were thinking of quitting within the next 30 days were encouraged to set a quit date with the telephone counselor and to check back to let the counselor know how they were doing. They were also given messages on how to become aware of when and why they smoked, in preparation for quitting. Callers in the action stage, that is those who were in the process of quitting, were given supportive messages about cessation and tips on things they could do to reduce the discomforts of quitting. Smokers in the maintenance stage who had "slipped" by smoking one cigarette were given messages to reinforce the idea that a slip was not equivalent to a full relapse and that they could easily resume their nonsmoking status. In summary, this group received more individualized responses to their concerns and questions and were always encouraged to take yet another step in the cessation process.

Hypotheses

We believed that providing more specific and appropriate information would be more likely to lead to behavior change. We hypothesized, therefore, that the stage-model approach to counseling would be more effective in promoting smoking cessation than the general-information approach. In addition, because the stage model provides messages designed to move smokers along the cessation continuum (for example, from contemplation to action), we hypothesized that smokers in this arm would move more quickly through the continuum than those in the general-information arm.

Adaptation of the CIS Stage-Model Protocol

Although the two intervention protocols provided a base from which to work, neither had been designed for a particular target group, such as blue-collar workers. Because limited information was available on messages that appeal to blue-collar workers who smoke, focus groups were formed to evaluate and adapt messages in the existing stage-model intervention protocol to make it more pertinent to that subpopulation. Two of the three focus groups were drawn from blue-collar workers who smoked and who were not employed at any of the work sites selected for recruitment of subjects. The first of these focus groups reacted generally to the intervention protocol and made suggestions for prioritizing, adapting, and adding new messages to the existing stage-based messages. These suggestions were incorporated and presented to the

second focus group of blue-collar workers. That group made additional changes in the wording of the counseling statements and emphasized the importance of the supportive role that telephone counselors should provide. The group advised that only ex-smokers be used as counselors because they could relate to the problems smokers have during cessation. A general theme that emerged was that smokers would want to know that counselors were listening to them and responding to their concerns, rather than delivering a script. Accordingly, more open-ended questions and opportunities for feedback from callers were incorporated in the protocol. A third focus group was made up of both blue-collar workers and white-collar workers who smoked and who were not employed at the recruitment work sites; this group reviewed the revised protocol for tone and content. A few minor revisions were made, and the group agreed that the final modified protocol was appropriate and attentive to the needs of blue-collar workers who smoke and could also be used with white-collar workers who smoke.

METHODS

Study Design

A two-armed, randomized control design was used in this study. Callers to a special hotline established for this study were advised of the nature of the intervention, asked to give oral informed consent, and given a telephone-administered baseline assessment of smoking characteristics, stage in the cessation process, intention to quit, level of addiction, and demographic characteristics. Smokers who agreed to participate were then randomly assigned to receive either the stage-based counseling protocol adapted for use in a blue-collar population or the general-information protocol.

Regular telephone follow-up of subjects was conducted at 1 month, 6 months, and for a subset of the volunteers recruited early in the study, 12 months after their initial call to the telephone hotline. Three methods were used to ascertain final smoking status. Subjects' self-reporting of quitting was supplemented with a request to mail in a saliva sample. These samples served as a "bogus pipeline" (18) because funds were not available to analyze them. In addition, surrogates were contacted and asked about the smoking status of self-reported quitters. (At enrollment, smokers were asked to designate one person who would be able to talk about their smoking habit.) For these analyses, nonsmokers were defined as those who reported abstinence from cigarettes at the 6-month follow-up call.

Procedures for Implementing the Intervention

Telephone counselors for this study were trained in the use of the two intervention protocols. Telephone staff were given scripts for the stage-model counseling and response sheets for the general-information counseling. They were also extensively rehearsed in the use of both of the intervention protocols. Existing CIS training practices were fol-

lowed and normal CIS quality-control procedures were used to ensure consistent delivery of both interventions. Quality control included random monitoring of telephone calls (approximately 10% of calls were monitored by the study director), as well as regular staff meetings to discuss issues and problems that arose in the counseling protocols. In addition, telephone staff were taught to administer a telephone version of the baseline questionnaire and were introduced to the follow-up questionnaires as well as strategies for reaching subjects for follow-up information.

Recruitment

Beginning in June 1988, four predominantly blue-collar work sites were recruited as channels for reaching blue-collar workers who smoke. Characteristics of and differences among these work sites have been reported previously (19). Low recruitment rates required us to enroll callers from other sources. Callers were identified as blue-collar workers or white-collar workers on the basis of job title, as classified by the major census definitions. Some callers were classified as "other" because they did not fit the major census definitions of blue- and white-collar workers; these included students who worked, retired people who worked part time, and the unemployed.

Our smoking-cessation information hotline was presented as a free service that was part of a study by the Fred Hutchinson Cancer Research Center, a well-known local institution. The service's independence from work-site management was emphasized, as was the confidentiality of the information obtained from callers. Hours of telephone-counselor availability were chosen on the advice of work-site health-promotion staff and then were adjusted to match times of most use; those who called after hours could leave a message and be called back. Promotion of the service used existing and readily available work-site communication channels.

Midway through the project it became apparent that a sufficient number of blue-collar smokers could not be recruited from among the workers at the four sites to satisfy the power calculations for detecting a difference in the two intervention arms. In March 1989, access to the hotline was broadened to further increase recruitment. Adults calling the local CIS office for help with quitting smoking or maintaining cessation were given the chance to be transferred to our hotline and participate in the study. In June 1989, the general public was also invited to use the hotline. Smokers were recruited through posters in community medical clinics, fliers placed in supermarkets and laundromats, and paid advertisements in a local newspaper. Call volume increased following the advertisements, as has been observed in other settings (20).

RESULTS

Subject Characteristics

In all, 382 eligible callers were enrolled in the study. Ninety-three callers (24.3%) were blue-collar workers, 181

(47.4%) were white-collar workers, and 108 were classified in the "other" category. (Of the 108 callers in the last group, the 63 unemployed subjects were not included in our analyses involving occupational status.) The general-information group contained 185 subjects; the stage-model group contained 197.

Predominantly, the callers were female ($N = 224$, 58.6%), married ($N = 190$, 49.7%), and had some college or trade-school training ($N = 175$, 45.8%) but were not college graduates. In these categories, only the percentage of females showed a statistically significant difference between the general-information and stage-model groups; the general-information group contained more females (120 versus 104 in the stage-model group) ($\chi^2 = 7.1$, $df = 2$, $P = .03$). The mean age of the 382 subjects was 40.6 years.

Table 1 presents the smoking characteristics of the callers by randomization to group.

A small number of callers ($N = 41$, 10.7%) were non-smokers at the time they called and were seeking relapse-

prevention assistance; the remainder were current smokers. Of the 341 current smokers, 47.5% reported smoking their first cigarette within 10 minutes of awakening, indicating that they were heavily addicted. The majority of all callers ($N = 251$, 65.7%) were in the contemplation stage of cessation. All callers had begun smoking in their teens, at a mean age of 17.2. The age of onset was lower for the general-information group, which also had a higher average number of pack-years per caller. Current smokers smoked an average of 18 cigarettes per day on a workday and 22 per day on a nonworkday. A mean of seven to eight previous quit attempts had been made, and the large standard deviation (28.7) indicates that some smokers had made very many quit attempts. Smokers in the stage-model group had on average made more serious quit attempts. When current smokers were asked about confidence in their ability to quit, the mean rating was 5.3 on a 10-point scale, where 1 is "not at all confident" and 10 is "extremely confident."

Table 1. Smoking characteristics, by randomized group

Variable	Stage-model group	General-information group	Total
	Categorical values*		
Level of addiction†			
< 10 min	88 (44.7)	74 (40.0)	162 (42.4)
10-30 min	43 (21.8)	40 (21.6)	83 (21.7)
31-60 min	22 (11.2)	27 (14.6)	49 (12.8)
> 60 min	27 (13.7)	18 (9.7)	45 (11.8)
Not applicable	16 (8.1)	25 (13.5)	41 (10.7)
Missing‡	1 (0.5)	22 (11.3)	2 (0.5)
Stage			
Contemplation	130 (66.0)	121 (65.4)	251 (65.7)
Action (quit date set)	43 (21.8)	37 (20.0)	80 (20.9)
Action (initial quit attempted)	4 (2.0)	7 (3.8)	11 (2.9)
Maintenance	12 (6.1)	18 (9.7)	30 (7.9)
Relapse	1 (0.5)	2 (1.1)	3 (0.8)
Missing‡	7 (3.0)	0 (0.0)	7 (1.6)
	Interval values*		
All callers			
Mean age first smoked§	17.8 (5.3)	16.5 (4.6)	17.2 (5.1)
Missing	7	0	7
Pack-years	21.7 (17.9)	24.3 (20.9)	22.9 (19.4)
Missing	7	0	7
Quit attempts¶	9.2 (38.7)	5.9 (10.4)	7.6 (28.7)
Missing	2	2	4
Current smokers			
Confidence in ability to quit#	5.5 (2.6)	5.1 (2.8)	5.3 (2.7)
Missing	0	0	0
Cigarettes smoked at work per d	18.2 (13.3)	18.1 (12.2)	18.2 (12.8)
Missing	0	0	0
Cigarettes smoked off work per d	22.8 (12.6)	21.1 (11.8)	21.9 (12.2)
Missing	0	0	0

*Unless otherwise noted, categorical values = No. of subjects and values in parentheses are %; interval values = means and standard deviations.

†Time between awakening and first cigarette.

‡This varies by variable—reported for categorical/ordinal data; excluded in calculating interval data.

§ $f = 1.31$, $P = .07$.

|| $f = 1.35$, $P = .05$.

¶ $f = 1.8$, $P < .001$.

#Ten-point scale: 1 = "not at all confident"; 10 = "extremely confident."

Recruitment Sources

The sources of recruitment of subjects are presented in Table 2. Smokers recruited from work sites and those recruited by newspaper advertisements were more likely to be randomly assigned to the stage-model group; callers recruited from the CIS and "other" sources were more likely to be randomly assigned to the general-information group. This difference most likely occurred because the computer-generated randomization scheme produced assignments based on an ideal sample of 400 subjects. When it was obvious that work-site recruitment would not yield that number, the second stage of recruitment, drawing subjects from the CIS, began; following that, the third wave of recruitment using newspapers and other media was initiated. Because we had not anticipated such recruitment difficulties, we did not plan for a balanced randomization and, thus, it is quite possible that for the small numbers recruited from each source, disproportionate assignment to each condition could have happened by chance. It is important to note that overall, however, the numbers randomized to each condition were equivalent.

Differences in characteristics of subjects by recruitment source have been reported elsewhere (19); in our study, statistically significant differences were found in age ($F = 12.4$; $P < .001$), with newspaper responders more likely to be older than responders from the other sources; education ($\chi^2 = 40.1$; $df = 15$; $P < .001$), with newspaper responders more likely to have more years of education; and blue-collar versus white-collar status ($\chi^2 = 69.6$; $df = 6$; $P < .001$), with newspaper responders less likely to be blue-collar workers.

Response Rates and Intervention Outcomes

Follow-up response rates were generally high: 92.1% at 1 month, 83% at 6 months, and 75.8% for those who were eligible for the 12-month follow-up. Because recruitment was an ongoing process throughout the study, only 207 of

the 382 participants had been enrolled for an entire year and, thus, were eligible for the 12-month follow-up. Examination of response rates by recruitment source and randomized group indicated no statistically significant differences for either the 1-month or the 6-month follow-up. Numbers for the 12-month follow-up became too small per cell to allow meaningful comparisons.

Nonsmoking prevalence at each of the follow-up points is presented in Table 3.

There were no statistically significant differences in nonsmoking rates between the two arms at any of the follow-up points. Overall nonsmoking rates were fairly high, ranging from 18.3% at the 1-month follow-up to 19.4% at the 6-month follow-up and 18.8% for those eligible for the 12-month follow-up. Unlike the results in other studies (9), there was no statistically significant drop in nonsmoking rates between the 1-month and 6-month follow-up. There was no statistically significant difference in nonsmoking rates between white-collar, blue-collar, and other subjects at the first follow-up, but by the 6-month follow-up, 22.9% of white-collar workers, 16.7% of blue-collar workers, and 42.4% of those in the "other" category remained nonsmokers. This difference was statistically significant ($\chi^2 = 8.6$; $df = 2$; $P = .01$).

We had hypothesized that use of the stage model of cessation counseling would result in smokers moving more rapidly through the stages of change in the cessation process. To test this hypothesis, stages were arrayed on a linear scale, and a change score (ranging from -3 to +3) was computed, indicating the average number of stages individuals in the stage-model and general-information groups traversed between follow-ups. Average change scores for the time between baseline and the 1-month follow-up were 0.27 and 0.21, respectively, for the stage-model approach and the general-information approach, 0.05 and -0.01 between the 1-month and 6-month follow-ups, and 0.32 and 0.20 for the entire period (baseline to 6-month follow-up). None of these differences was statis-

Table 2. Recruitment source, by randomized group*

Source	Group, No. of subjects (%)		Total, No. of subjects (%)
	Stage-model	General-information	
Work-site recruitment	40 (20.3)	27 (14.6)	67 (17.5)
Newspaper advertisements	79 (40.1)	62 (33.5)	141 (36.9)
Calls referred from the CIS	70 (35.5)	75 (40.5)	145 (38.0)
Other†	8 (4.1)	21 (11.4)	29 (7.6)

* $\chi^2 = 10.2$, $df = 3$, $P = .02$.

†Refers to posters in medical clinics and fliers hung in supermarkets and laundromats.

Table 3. Self-reported nonsmoking rates, by randomized group

Follow-up	Group, No. of subjects (%)		
	Stage-model	General-information	Overall
1 month	33 (16.8)	37 (20.0)	70 (18.3)
6 months	40 (20.3)	34 (18.4)	74 (19.4)
12 months (No. eligible = 207)	19 (19.2)	20 (18.5)	39 (18.8)

tically significant. For the same three follow-up periods, we examined the proportion of smokers reporting positive movement along the stages of change and saw no differences between the two trial arms.

Self-reports of smoking status at the final follow-up point (6 or 12 months, depending on how long the subject had been in the study) were substantiated by reports of one surrogate per self-reported nonsmoker, with almost unanimous agreement between the self-reports and the surrogate reports.

DISCUSSION

This study was initially directed at blue-collar workers who smoke. It proved difficult to recruit blue-collar workers, and of the final subject pool, only 24.3% were classified as blue collar. The recruitment difficulties we experienced were consistent with those of others who attempted to recruit blue collar workers who smoke (2). As in other studies (5,21,22), our results show that of the blue-collar workers enrolled, fewer were able to maintain their nonsmoking status, compared with white-collar workers. It is notable, however, that 16.7% of the blue-collar subjects were nonsmokers at the time of the 6-month follow-up. This rate is higher than that reported for minimally assisted cessation in the general population (9) and has favorable public-health implications.

This study was intended to examine the relative efficacy of two different approaches to telephone smoking-cessation counseling. We found few statistically significant differences between the groups randomly assigned to the different intervention protocols with regard to demographic or smoking characteristics. There were no statistically significant differences in either short-term (1-month) or long-term (6-month) nonsmoking rates between the groups. The rate of nonsmoking, however, was high: nearly 20% of all callers reported not smoking at each of the follow-up points. Confidence in the self-reports is indicated by high agreement with surrogate reports.

Two hypotheses had guided the development of the experimental intervention. The first was that stage-based advice and counseling on smoking cessation was more likely to be effective in assisting smokers in achieving cessation than was providing general information. The second was that stage-based advice and counseling would move smokers faster through the process of smoking cessation than general information.

The first hypothesis was not supported. Smokers who received general advice were as likely to become nonsmokers as those receiving the staged advice. This is contrary to theoretical positions (16,17) as well as the current tendency toward development of stage-based materials. A possible explanation may lie in an opinion expressed in one of the focus groups: smokers are more likely to want general encouragement, answers to their specific questions, and a "friendly ear" than an elaborate protocol that teaches them how to achieve cessation. Providing general information and answers to questions, as was

done in one arm of the present study, may provide those features as well as a stage-based counseling approach does. It may also be that this group of 382 smokers was very motivated, with the great majority in the contemplation stage and ready to attempt cessation. Given a high level of motivation, it may be that nuances in the counseling procedures are irrelevant. Previous studies that provided other forms of minimal assistance (e.g., self-help manuals) showed lower overall cessation rates; the results of 10 long-term prospective studies on self-quitting, or quitting with only minimal assistance, indicate that, with the exception of one study center, 4.6%–7.7% of individuals in the 10 study sites quit on their own or with minimal assistance (9). Our results surpass those figures and suggest that telephone counseling is a useful method to stimulate smoking cessation. The support and encouragement provided by a counselor may be responsible for the higher than normal nonsmoking rates in both groups.

The second hypothesis also was not supported. In this analysis, we examined what happened to the smokers under the two protocols at each of the follow-up points; we saw no differences between the two groups in movement through the cessation stages, even from contemplation to action, although both groups had made some small move along the continuum between baseline and 6 months. Information on the time required to move smokers to subsequent stages of cessation is sparse (23), and it is unclear whether enough time elapsed in the present study to achieve movement through the process. There is also evidence that smokers shift back and forth between stages (23) and that an examination of an entire group may conceal movement by individuals. It is also likely that smokers did not have sufficient exposure to messages oriented to moving them through stages of cessation. Only a few subjects called the line a second time; thus, the majority of smokers had only one opportunity to receive cessation messages.

From a cost perspective, the stage-based counseling, at least as practiced in this research setting, is more time consuming (average time of call = 34 minutes) than the provision of simple information (average time of call = 20 minutes); given that there is no difference in outcome between the two, it may be worthwhile to return to the method that is less costly. On the other hand, the telephone staffers were more satisfied with the stage-based model because it gave them specific directions for responding to callers' questions about smoking. It may be important to conduct a cost analysis of the two approaches independent of the requirements of a research setting.

An important consideration of the present study involves the sources of recruitment of smokers. More smokers were recruited to the hotline through newspaper advertisements than by any other means, suggesting that this is a useful avenue for recruitment. Although more expensive—recruitment cost of \$198.23 per quitter (19)—than the cost of recruiting via the CIS (considered to be zero cost because smokers who called were simply routed to our project), it still appears to be a reasonable cost, espe-

cially if a local CIS office is interested in conducting a campaign targeted to specific groups. Such campaigns have been conducted previously with high caller-response rates (20). More detailed summaries of the recruitment costs of this project have been reported elsewhere (19).

In summary, this study showed no difference between a stage-based smoking-cessation counseling approach and a general-information approach within a telephone hotline setting. It supports a general finding in the smoking-cessation literature that slight differences in intervention messages and materials are unlikely to produce statistically significant differences in nonsmoking rates (1). It is not yet clear under what circumstances, if any, the stage-model approach will accelerate the cessation rates of groups subjected to minimal interventions.

This study shows the difficulty of recruiting blue-collar workers, at least through work-site channels, to make use of telephone smoking-cessation hotlines (24). Other studies have identified similar results in recruiting smokers in general to hotlines. The challenge of reaching blue-collar workers who smoke and finding simple ways to assist them in achieving cessation has not been met through this method, largely because of the lack of success in recruiting blue-collar workers to use the service. Further research is needed to address the recruitment and cessation needs of this high-prevalence group of smokers.

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Results of an Antismoking Media Campaign Utilizing the Cancer Information Service

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In this paper, results are presented on the response to an antismoking media campaign designed to encourage women cigarette smokers with young children to call for information on quitting. The intervention campaign used a mix of professionally produced broadcast and print materials that encouraged smokers to call the National Cancer Institute's Cancer Information Service (CIS) for information on quitting. The campaign was implemented in seven media markets in New York state, Pennsylvania, and Delaware; each of these markets was paired with a control market in one of the three states. Response to the campaign was gauged by monitoring calls to the New York and Pennsylvania area CIS offices from smokers residing in intervention and control media markets. Results from the 46-week campaign show that the number of calls for smoking-cessation information was five times greater from intervention markets than from control markets. The campaign also was successful in reaching the target audience of mothers of young children. Twenty-nine percent of calls received from intervention markets were from the target audience compared with 10% from the control markets. Forty-four percent of all calls received from intervention markets came during a 5-week period when time was purchased to air television spots. [Monogr Natl Cancer Inst, 14:113-118, 1993]

OVERVIEW

The communications literature suggests that the effectiveness of persuasive messages can be enhanced by tailoring the message to the characteristics of the intended receiver (1-4). The purpose of our study was to test the value of using targeted communications to motivate and assist cigarette smokers to stop smoking. The target group for this research was women cigarette smokers with young children. This group was selected because young women have been specifically identified as the target of tobacco industry advertising campaign efforts (5-7). Moreover, since 1980, smoking rates among young adult women have remained relatively stable while smoking rates among males and older females have dropped steadily (8). Additionally, a mother's smoking places her children at risk of developing a wide range of respiratory ailments as a result of exposure to environmental tobacco smoke (9).

This paper describes the final results from an intervention study that tested the impact of a targeted mass-media campaign designed to motivate smokers to call the Na-

tional Cancer Institute's (NCI's) Cancer Information Service (CIS) for information on stopping smoking. Our previous paper (10) described the design of the study and reported results from the first 28 weeks of the 46-week media campaign. The reader is referred to that paper for a detailed description of the study methods and materials.

METHODS

This study utilized a posttest-only control-group design. The units of analysis were individual media markets located in New York state, Pennsylvania, and Delaware. Media markets were defined according to television areas of dominant influence (11). Selection of media markets was restricted to the geographic regions served by the CIS offices at Fox Chase Cancer Center and Roswell Park Cancer Institute. In this geographic region, there are 16 separate media markets, nine in New York state, six in Pennsylvania, and one in Delaware. Two media markets, Binghamton and Utica, New York, were excluded from this study because of their involvement in another NCI-sponsored study on smoking cessation. The remaining 14 media markets were matched on the basis of population size, yielding seven matched pairs (see Table 1). In each matched pair, one market was randomly assigned to be exposed to the intervention campaign. The campaign was withheld from the control markets, but no effort was made to inhibit other CIS advertising, some of which was smoking related.

Response to the campaign was gauged by monitoring the number of calls to the New York and Pennsylvania area CIS offices from smokers residing in intervention and control media markets. (Fox Chase Cancer Center covered the Delaware control media market.) Callers gained access to the CIS by dialing 1-800-4-CANCER. During the period of the campaign, CIS counselors completed a Call Record Form (CRF) for every smoking-related inquiry. The CRF collected information on the demographic characteristics of callers, address, smoking status, and whether the caller was part of the target audience (i.e., a mother with a young child). To be considered part of the target audience callers had to respond positively to the following five questions:

*See "Notes" section following "References."

- Are you a smoker?
- Are you female?
- Do you have any children?
- Do you have any children under age 6?
- Would you like a free booklet about quitting smoking on your own?

A list of ZIP codes grouped according to each of the 14 media markets in the study was compiled so that callers could be assigned to media markets on the basis of their ZIP codes.

The Campaign

The campaign used a mix of professionally produced broadcast and print materials encouraging smokers to telephone the CIS for information on quitting smoking. Television was chosen as the primary vehicle for reaching smokers in targeted communities based on previous experience in promoting the CIS (12-14). An advertising company was retained to develop campaign materials and advise investigators regarding implementation of the campaign. In developing campaign materials and television spots, a number of steps were followed. Initially, investigators met with staff from the advertising company to discuss campaign themes and concepts. From these initial discussions, six storyboards were developed as potential ideas for television spots. The storyboards were presented to a focus group of 10 mothers (all smokers) of young children. Participants were asked to identify which storyboards they preferred and to offer suggestions about what kind of messages might encourage them to consider stopping smoking. The initial storyboards included an array of concepts ranging from a focus on the health effects of smoking on the active smoker to the health dangers that a mother's smoking poses to her children. The results of the focus-group interviews suggested that messages about the dangers of secondhand smoke to young children would be most likely to elicit a response from the target audience. "Give Them Breathing Room" was adopted as the overall campaign theme, and television spots that highlighted the dangers of secondhand smoke were produced. Below is a description of the three 30-second television spots that were developed as part of the campaign.

• *Spot 1: "Smoking Head."* The back of a woman's head is seen silhouetted in medium close-up. She has long hair over her shoulders and a lighted cigarette is held in her right hand. The hand moves to the mouth and a puff of smoke rises into the air. The narrator's voice is heard, saying: "Tobacco smoke contains many toxic chemicals; some cause cancer. Because their little lungs breathe faster, children inhale more secondhand smoke than do adults." The narrator pauses. As the "woman" slowly turns, the music rises and lights come up to reveal a little girl holding a lighted cigarette. The voice-over continues: "So if you smoke, it's as if your children are smoking, too. Secondhand smoke causes pneumonia, bronchitis, asthma, and other health problems in children. Give them breathing room." The CIS, 1-800-4-CANCER

number appears, and the narrator continues, "Call now; we can help you break your smoking habit."

• *Spot 2: "Pediatrician's Office."* The scene is a pediatrician's office. A doctor examines a young boy as we hear the mother say: "... and he's had all these ear infections—seems like every month he gets another one—and he coughs all the time. Does that have anything to do with the bronchitis he had last year?" The doctor thinks a moment and asks: "Do you smoke?" The mother, her eyes downcast, pushes a cigarette pack into her black purse as the camera zooms in on it. The CIS number is superimposed over the purse. The narrator's voice is heard, saying: "Secondhand smoke causes pneumonia, bronchitis, asthma, and other health problems in children. Give them breathing room. Call now; we can help you break your smoking habit."

• *Spot 3: "New Year's Resolution."* A mother is sitting on a living room couch smoking a cigarette. New Year's Eve party decorations dress the set. The mother speaks to the camera and the music of "Auld Lang Syne" is heard softly in the background. "Every New Year's Eve I make a resolution to quit smoking. I never do it." The camera zooms in as she puts out her cigarette. She continues to speak: "But this year I've got one very important little reason to stop." The mother picks up her baby as the camera zooms in. The mother continues talking: "My doctor told me cigarette smoke could hurt my baby. He said it can cause earaches, stuffy nose, wheezing, and other health problems. Then he told me about an 800 number I can call to talk with people who are ready to help me stop smoking." The next frame shows a phone being dialed and ringing with the CIS number superimposed on the screen. A voice is heard answering the phone: "Cancer Information Service. Can we help you?"

For the most part, the television spots were aired as public service announcements. In an effort to encourage television stations to play the spots, each station was personally visited by project staff who delivered the tape and offered to discuss the campaign with the station's public service director. In addition, several times during the campaign, stations were contacted by phone and asked about their use of the television spots. In several cases, new tapes were mailed to the stations because follow-up revealed that originals had been lost or destroyed.

In three periods during the 46-week campaign, television time was purchased in each of the intervention markets. This was done to ensure adequate exposure of the target audience to the campaign messages, as well as to evaluate potential benefits of purchasing air time. The first buy occurred during the third week of September, when the "Smoking Head" and "Pediatrician's Office" spots were aired. The second buy occurred in early January and used the "New Year's Resolution" spot. The third buy occurred during the middle 2 weeks of May to correspond with Mother's Day. During the third buy, the "Smoking Head" and "Pediatrician's Office" spots were aired.

In all instances, purchases were structured to achieve equal audience penetration in each market, as measured in

gross rating points. Gross rating points provide a crude measure of the percentage of the target population exposed to the message. One gross rating point is equivalent to exposing roughly 1% of the target population to the message one time. One hundred gross rating points translates into reaching 100 members of the target population with the message one time, though of course some will see the message more than once and others, not at all. Specific time slots purchased were selected to optimize exposure of the campaign messages to young-adult females (ages 18–34 years).

In addition to the television spots, an array of supporting print materials was developed. These included not only press releases but also a pamphlet and a poster, which were distributed to health-care providers in each of the target markets. Public service announcements were distributed to radio stations. In each market, the campaign was initiated through a local press conference, and an effort was made to localize the campaign by working with a recognized volunteer agency (the American Cancer Society in New York, the American Lung Association in Pennsylvania). The campaign evaluation covered a 46-week period beginning in the last week of July 1988 and ending in mid-June 1989.

Analysis Plan

The units of analysis in this study were the seven media market pairs. Differences between intervention and control markets were tested using the Wilcoxon matched pairs signed rank test. The *P* values presented are based on two-tailed tests of significance.

RESULTS

During the 46 weeks of the campaign, the CIS received 2954 calls from persons who sought smoking-cessation information and who resided in either intervention or control media markets. Table 1 provides a breakdown of the total number of calls received, calls received from smokers, and the percentage of calls from the target audience by media market. Combined, the intervention markets accounted for 4.8 times as many calls as did the control markets. The call rate per 10 000 smokers was significantly higher in intervention markets compared with controls ($P < .01$) and was 6.9 times greater overall. In intervention markets, 28.9% of calls received were from the target audience compared with 9.5% in control markets ($P < .01$).

The demographic characteristics of callers are shown in Table 2. Table 2 also shows how callers found out about the CIS. A greater percentage of callers from intervention markets were between the ages of 20 and 29 compared with callers from control markets ($P < .01$). Callers from intervention markets were also more likely to be female compared with callers from control markets ($P < .01$). Television was cited as the primary source of learning about the CIS by the majority of callers in both intervention and control markets. A slightly higher percentage of callers from intervention markets reported learning about the CIS from television compared with callers from control markets.

Fig. 1 shows the number of calls received per week. In intervention markets, the number of calls increased mark-

Table 1. Summary of calls received, by media market pairs

Media market	Status*	Estimated No. of adult smokers	Total No. of calls for smoking information	No. of calls from smokers	No. of calls from smokers per 10 000 smokers in the population	No. of calls from target group	Percentage of calls from the target group
Pittsburgh, Pa.	I	771 208	799	696	9.02	227	28.4
Philadelphia, Pa.	C	1 675 927	281	238	1.42	23	8.2
Buffalo, N.Y.	I	389 707	758	621	15.93	190	25.1
Harrisburg, Pa.	C	320 915	78	68	2.12	8	10.3
Wilkes-Barre, Pa.	I	268 477	314	282	10.50	98	31.2
Albany, N.Y.	C	303 397	36	29	0.96	3	8.3
Syracuse, N.Y.	I	236 292	189	154	6.52	63	33.3
Rochester, N.Y.	C	217 202	42	31	1.43	9	21.4
Johnstown, Pa.	I	179 896	208	184	10.23	68	32.7
Erie, Pa.	C	93 700	36	29	3.09	4	11.1
Elmira, N.Y.	I	52 380	68	56	10.69	23	33.8
Wilmington, Del.	C	81 771	26	25	3.05	1	3.8
Watertown, N.Y.	I	50 809	112	101	19.88	39	34.8
Plattsburgh, N.Y.	C	34 920	7	6	1.72	0	0.0
Total	I	1 948 769	2448	2094	10.74	708	28.9
	C	2 727 832	506	426	1.56	48	9.5

*I = intervention group; C = control group.

Table 2. Demographic characteristics and reported source of information about the CIS from callers in intervention and control markets

Demographic characteristic	All intervention markets, % (n = 2448)	All control markets, % (n = 506)
Age, y		
≤ 19	8.5	9.7
20-29	36.4	23.8
30-39	30.1	25.5
40-49	12.6	16.3
50-59	6.8	11.8
≥ 60	5.6	12.9
Sex		
Male	21.9	31.2
Female	78.1	68.8
Race		
White	93.4	90.9
Nonwhite	6.6	9.1
Education		
Some high school	14.9	12.3
High-school graduate	51.8	53.6
Some college	22.6	16.8
College graduate	10.7	17.3
How found out about the CIS		
Television	71.5	57.7
Radio	2.5	1.3
Newspaper	8.7	3.9
Poster/brochure	2.9	3.1
Other	14.4	34.0

edly with the purchase of television time and was related to the amount of time purchased. In September 1988, we purchased an average of 141 gross rating points per market over a 1-week period. In January 1989, we purchased an average of 292 gross rating points in each market but spread the purchase over a 2-week period. In May 1989, we purchased an average of 126 gross rating points per market spread over a 2-week period.

Combined, the three television buys accounted for 44% of all the calls received from intervention markets during the 46-week campaign. The proportion of the target audience responding to the campaign varied over time. During the September television buy, when the "Smoking Head" and "Pediatrician's Office" spots were aired, 47% of all calls were from the target audience. In January, when the "New Year's Resolution" spot was aired, 28% of all calls were from the target audience. In May, when television airtime was again purchased to air the "Smoking Head" and "Pediatrician's Office" spots, 26% of calls were from the target audience. During all other periods of the campaign, 27% of calls came from the target audience.

Follow-up interviews were conducted with a subsample of callers to determine the proportion who attempted cessation and stopped smoking. The subsample included only the target audience of mothers with young children. In all, 770 members of the target audience were eligible to be followed up regarding their smoking status. Of these, 719

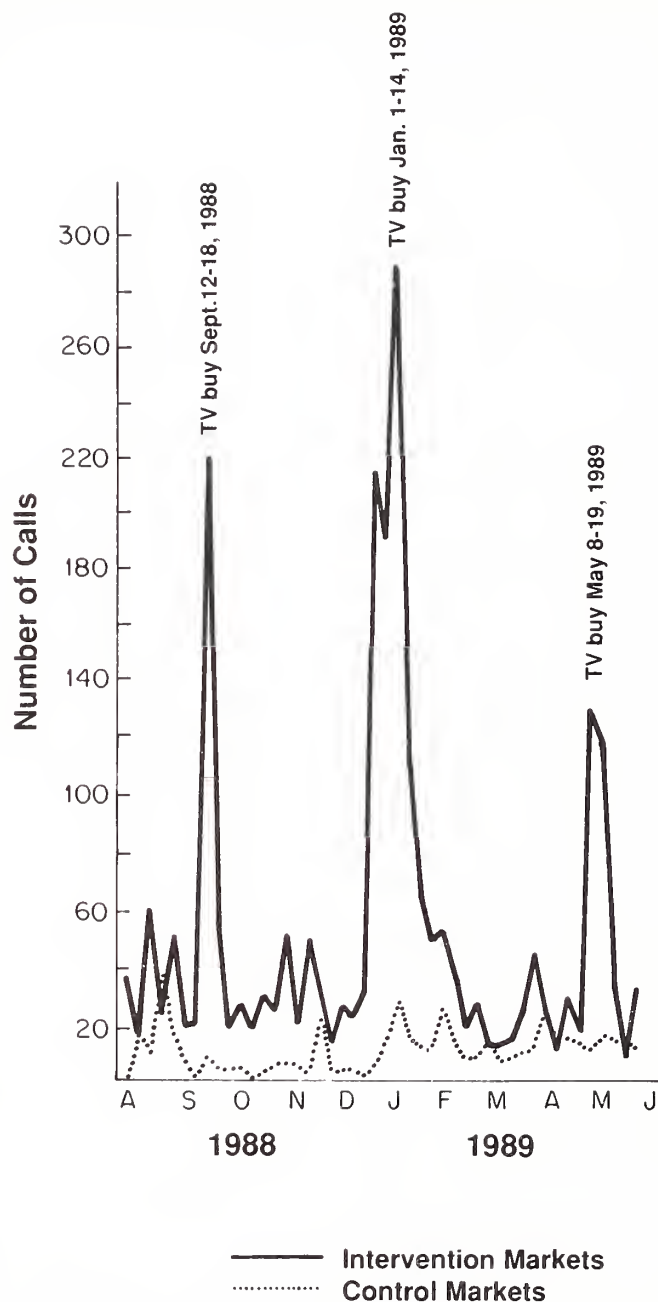


Fig. 1. Weekly call volume from smokers in intervention and control markets.

were from intervention markets and 48 were from control markets. Six-month follow-up interviews were completed with 559 (73%) of the 770 women. Response rates were similar in intervention and control markets. Overall, 63% of the women who were followed up reported making an attempt to stop smoking. Attempts at quitting were slightly higher among women calling from intervention markets compared with those calling from control markets (64% versus 46%; $P = .06$). Of the 559 women who were contacted for the 6-month interview, 72 (13%) reported that they had quit smoking and had not had a cigarette for at least a week at the time of the 6-month follow-up

interview. The quit rate among callers from intervention markets was 13% compared with 15% among callers from control markets ($P = .89$).

CONCLUSIONS

This study shows that the media campaign was successful in increasing the number of smokers calling the CIS for information on quitting. This finding is consistent with results from other studies (14-16) which have used requests for smoking-cessation information to measure response to mass-media promotions. Unlike previous studies, however, the use of control media markets in this study makes it possible to estimate the level of response to the campaign. Not surprisingly, in both intervention and control markets, less than 1% of smokers actually called the CIS for information on quitting. In intervention markets, however, the overall call response from smokers was consistently higher in every market compared with control markets. With 50 million smokers in the United States, the campaign, if applied nationwide, could result in an estimated 45 900 *additional* calls per year to the CIS from smokers seeking information on quitting.

In addition to increasing the number of smokers calling the CIS, the campaign was also successful in reaching the target audience of mothers with young children. The proportion of callers representing the target audience was greater in each intervention market when compared with its control.

The greater response from the target audience in intervention markets cannot be attributed solely to the purchase of advertising time or specific messages. Although call volume from all smokers increased dramatically during periods when advertising time was purchased, the percentage of the calls that were from the target audience was fairly constant throughout the 46-week campaign and was consistently higher in intervention compared with control markets. The one exception to this occurred during the 3rd week of September when advertising time was first purchased and the percentage of the target audience calling the CIS was significantly higher (47% versus 26%; $P < .01$) than during other periods of the campaign. The greater response from the target audience during the September television buy cannot be attributed to the television spots used because the same spots were used during the advertising buy in May. The specific time slots purchased were similar for the September, January, and May advertising buys. The overall number of gross rating points purchased in each market was similar for the September and May advertising buys, but the intensity varied. In September, the advertising time was purchased for a 1-week period, but in May, the time slots were spread over a 2-week period. Also, the September advertising purchase occurred at the start of the campaign in contrast to the May advertising purchase.

Although many have advocated purchasing commercial time on television to air health-promotion messages, little empirical evidence is available to judge the value of paid

versus public service announcement time. This study shows very clearly the impact of purchasing time. Approximately 44% of all calls received from intervention markets during the 46 weeks of the campaign came during the 5 weeks when television advertising was purchased. Call volume was directly related to the level of advertising purchased.

Ideally, to evaluate the effect of paid versus public service advertising, the frequency with which messages are played should be known. Unfortunately, we found it impossible to document accurately the extent to which our spots were played as public service announcements. We contacted the 22 television stations that received our spots to request information about the number of times the spots had been aired and about the time of day during which they were aired. Nine of the stations reported that they could not provide specific information but did give rough estimates of the frequency of airing spots. Estimates ranged from once per day to one or two times per week. Five stations indicated that the spots were aired but provided no information on how frequently. Five stations reported that they never aired the spots as public service announcements. Two stations in Buffalo provided information on the frequency and timing of spots played as public service announcements between August 1988 and November 1988. These stations reported playing the spots two to five times per week, but half of the time, the message was aired between 12 AM and 7 AM, low viewership hours during which the CIS is closed.

In this study, we made a special effort to encourage television stations to play our spots as a public service. The amount of exposure given the spots probably reflects the optimum conditions for a public service campaign. Despite our efforts to motivate television stations to use the spots, our findings suggest that in most markets the spots were played only sporadically as public service announcements. Future research should examine the costs and effects associated with paid versus public service advertising.

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Proactive Screening Mammography Counseling Within the Cancer Information Service: Results From a Randomized Trial

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In 1987, the Division of Cancer Prevention and Control, National Cancer Institute (NCI), funded a randomized trial of a proactive counseling protocol to promote screening mammography among age-eligible female callers to the Cancer Information Service (CIS). This protocol included interactive counseling by CIS counselors to help callers overcome barriers to screening mammography; this counseling was an extension of usual service and was combined with a 2-week follow-up mailout to reinforce the brief (6-minute) proactive telephone-counseling protocol. The screening-mammography counseling intervention was tested in two regional CIS offices using a randomized two-group design. Callers were randomly assigned to the intervention or control group based on the week of their call to the CIS ($n = 1831$ eligible female callers). Self-reported adherence to NCI screening-mammography guidelines was assessed from telephone interviews conducted at 12 months' follow-up (87% response rate). Among all CIS callers enrolled in this study, self-reported adherence to screening-mammography guidelines at 12 months' follow-up was 63.5%. The most frequently cited barriers to screening mammography reported by CIS callers were inconvenience/being too busy (52%), cost (36%), lack of physician referral (34%), no symptoms (34%), and fear of radiation (29%). A significant intervention effect on adherence behavior was found but only in one of the two test sites and only among CIS callers reporting total family income of \$30 000 or more (odds ratio = 1.38, $P = .04$). The vast majority (90%) of CIS callers (both intervention and control subjects) endorsed the concept of proactive counseling by the CIS. The implications of these findings for the CIS and future research are discussed. [Monogr Natl Cancer Inst 14:119-129, 1993]

INTRODUCTION

Breast cancer will strike one in eight women in the United States, with an estimated 180 000 new cases and 46 000 fatalities in 1992 (1). These grim statistics underscore the fact that breast cancer is a major public-health problem in this country. With early diagnosis and treatment, however, breast cancer is highly treatable. Five-year survival rates for nonlocalized disease are currently below 60% but increase to 91% if the disease is detected and treated in a localized stage (1). It has been estimated that approximately one third of all deaths due to breast cancer

could be avoided with screening and early diagnosis using mammography combined with appropriate treatment (2,3). Despite the clear survival advantages attending adherence to screening-mammography guidelines, nonadherence to these guidelines remains a significant public-health problem (3-10).

The Cancer Information Service (CIS) of the National Cancer Institute (NCI) represents a potentially significant channel for reaching women eligible to receive a screening mammogram (11). The majority of callers to the CIS are female, White/Anglo, and of middle age (or older), which conforms to a population subgroup with elevated risk that would benefit from regular breast-cancer screening. If every CIS female caller over the age of 40 who is not a cancer patient and not calling about breast cancer were to be counseled *proactively* about mammography, that could amount to over 150 000 callers counseled per year (based on 1991 CIS call volume).

Current CIS policies and procedures do not include proactive counseling of age-eligible female callers about screening mammography. In 1987, however, NCI's Division of Cancer Prevention and Control funded a randomized trial of such a protocol as part of the Cancer Communications Systems Research (CCSR) program initiative. The final results of this study are reported below.

METHODOLOGY

Research Design

The research design of the CCSR study is presented in Fig. 1. As shown, eligible female callers were randomly assigned to one of two groups, based on the week of their call to the CIS ($N = 56$ weeks of subject accrual). Weeks were selected as the unit of randomization because a more intensive randomization protocol was considered to be too disruptive to normal CIS office routine. The control group ($n = 961$) was counseled according to usual or standard practice (i.e., no proactive counseling with respect to screening mammography). In contrast, the intervention group ($n = 870$) received both usual service and proactive screening-mammography counseling. Both groups were interviewed at 12 months' follow-up to deter-

*See "Notes" section following "References."

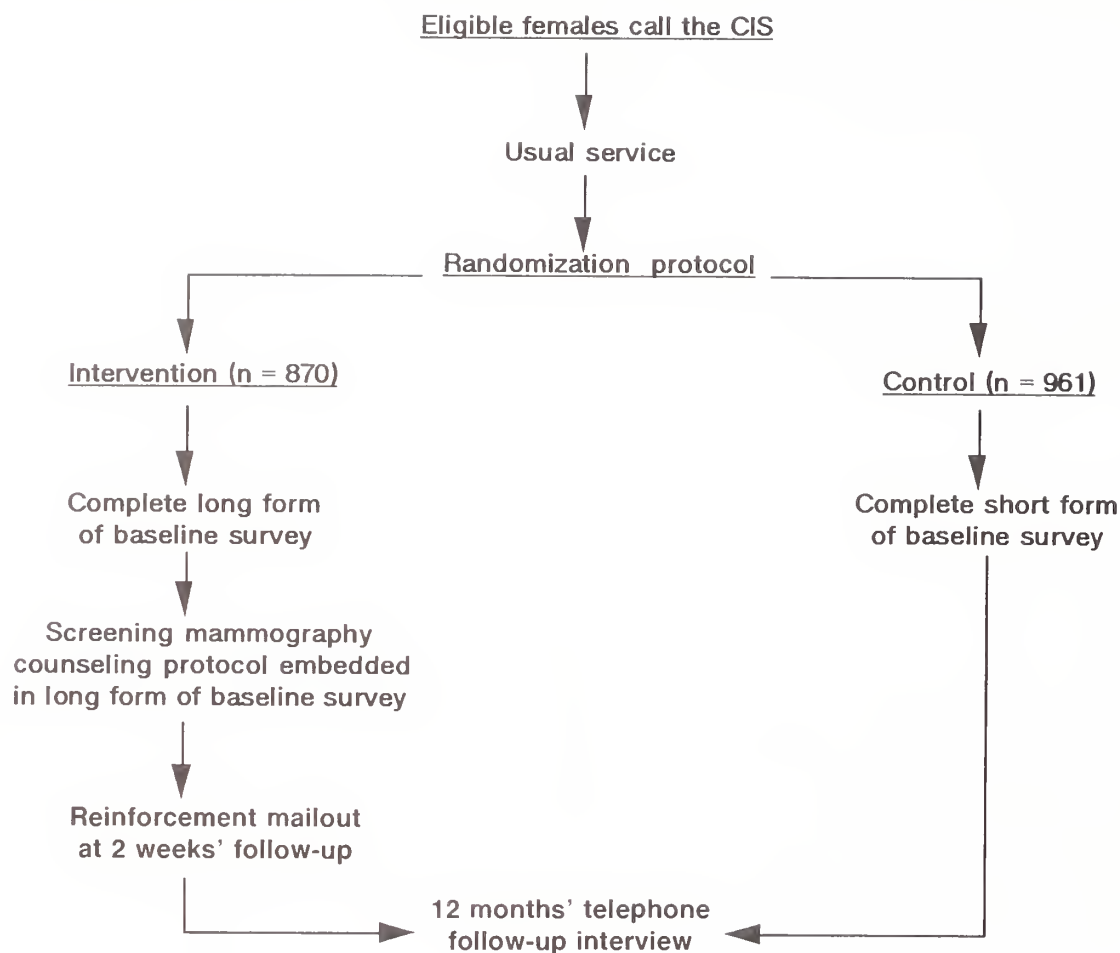


Fig. 1. Research design of the Cancer Communications Systems Research study.

mine their adherence to screening-mammography guidelines.

Eligibility Criteria

This study was conducted at two regional CIS offices (site A and site B) that collaborated in providing service to one of the largest states in the nation. CIS callers were considered eligible for enrollment in the study if they satisfied all of the following criteria:

- Female, 40+ years of age.
- Not calling about breast cancer or breast-cancer screening; no report of breast-cancer symptoms (e.g., a palpable breast lump).
- Not a cancer patient.
- No previous call to the CIS during the accrual period.

The age criterion listed above corresponds to the NCI guidelines for screening mammography. Callers making inquiries about breast cancer or breast-cancer screening and callers reporting breast-cancer symptoms (e.g., a palpable breast lump) were excluded under the presumption that they would normally receive information about

mammography as part of usual service. Cancer patients were excluded for several reasons: 1) their presumed higher levels of distress and preoccupation with their cancer when calling the CIS, which may make a prevention message appear inappropriate to the caller, 2) the fact that they were likely to be under more intensive medical surveillance for their cancer, and 3) because the counseling intervention was designed to target asymptomatic female callers to the CIS. Eligibility status was determined by CIS telephone counselors using a modified version of the Call Record Form (CRF), combined with a supplemental baseline survey appended to the CIS CRF (described below). Approximately 5% of otherwise eligible CIS callers were not enrolled in the study because they were emotionally distressed at the time of the call (based on the professional judgment of the CIS telephone counselors).

Overview of Screening-Mammography Counseling Protocol

The Screening-Mammography Counseling Protocol (SMCP) was delivered by CIS counselors as part of a

baseline survey appended to the CRF. Two versions of the baseline survey were conducted. During the control weeks, a short form of the interview was completed that 1) obtained additional information needed to determine caller eligibility (e.g., previous calls to the CIS during the period of sample accrual, cancer history); 2) asked for permission to conduct a brief telephone follow-up interview as part of a follow-up study of CIS users (i.e., the 12-month follow-up survey used to obtain the outcome measure in this study); and 3) asked callers to provide the name, telephone number, and address of two people who could help the CIS locate the caller for the follow-up survey (in the event that problems were encountered in this regard). It is instructive to note that a deliberate decision was made to avoid asking control subjects about their screening mammography behavior at baseline. This was done for two main reasons. First, there was concern that having CIS counselors ask such questions might sensitize callers to obtain a mammogram. More important, however, was the counsel and advice provided by the CIS counselors during the design phase of the project. If baseline rates of screening mammography were obtained for control subjects, CIS counselors indicated that they would feel compelled to counsel nonadherent callers. To do otherwise, we were told, would contradict their basic training and service-delivery instincts, as well as their overriding commitment to the public they serve. Accordingly, we opted for an "after-only" design for control subjects, in response to the strong preferences voiced by the CIS counselors participating in this study. It should also be noted that all nonadherent subjects (both intervention and control) were subsequently encouraged to obtain a screening mammogram at the conclusion of the 12-month follow-up interviews.

During the intervention weeks, a longer form of the baseline survey was conducted. The longer form included questions on screening mammography, as well as a question asking callers to indicate the likely barriers that might prevent them from obtaining a screening mammogram. This part of the survey was formatted as a checklist. Linked to each item on the checklist was a scripted response to be used (or paraphrased) by the counselor to provide counterarguments to the barriers reported by each caller. Table 1 presents the scripted responses that constituted this interactive behavioral counseling component of the SMCP. Also included in the long form of the baseline survey was a question asking callers if they would like a referral to a screening-mammography facility in their local area. If they answered yes, telephone counselors provided such referrals from the CIS referral directory. On average, the counseling protocol described above took about 6 minutes to complete. Fewer than 2% of eligible callers refused the baseline survey when their oral consent was solicited by the telephone counselors.

In addition to proactive behavioral counseling, the SMCP also included a follow-up mailout to eligible CIS callers assigned to the intervention condition. This mailout included a personalized thank-you note for using the CIS

(e.g., individually addressed, personally signed by the CIS coordinator); a two-sided bookmark that highlighted NCI guidelines for screening mammography and the need to adhere to these guidelines; and an attractive, multicolored information booklet on screening mammography which described the procedure, recommended guidelines, and explained why adherence to the guidelines is important. This mailout occurred approximately 2 weeks after the initial call to the CIS.

The SMCP has several distinctive features. First, because it was embedded within the long form of the baseline survey, the content of the behavioral-counseling message could be standardized and yet tailored to the responses of the individual caller. In addition, the format for delivering the intervention (i.e., as part of a telephone interview) represented a straightforward extension of the standard CIS CRF protocol. The SMCP did not require CIS counselors to master new skills or engage in fundamentally new activities. This method of formatting the intervention (i.e., as an extension of the CIS CRF interview) reflected our desire to integrate the SMCP into normal CIS office routine with minimal disruption. CIS counselors were also encouraged during the training program to "use their own words" when delivering the SMCP. This aspect of the training program proved to be quite successful—in large part because CIS counselors were already experienced at paraphrasing complex medical information for the lay public.

Another distinctive feature of the SMCP was the control it provided over the randomization protocol. By having the CIS office manager replace the short or long form of the baseline survey at the beginning of the appropriate intervention or control week, adherence to the randomization protocol was virtually assured. Accordingly, at the end of each intervention/control week, the CIS coordinators at both offices were contacted by project staff to remind them to replace the baseline surveys at the work stations of the counselors, according to protocol.

The SMCP was pilot tested at both sites for 1 week, followed by a debriefing session with CIS counselors. This pilot test included a 1-day training program consisting of overview presentations by the principal and co-principal investigators, role-playing exercises, and pretests on the telephone which were monitored by project staff. The pretest suggested no major changes in the research protocols, and, thus, the study proceeded directly to full-scale implementation at the two sites. During the early start-up phase of the project, adherence to protocol by the CIS counselors was monitored by the CIS office coordinator and/or the telephone supervisor at both sites. Such monitoring is a normal quality-control procedure within the CIS. As will be noted below, however, there is evidence to suggest that this monitoring/quality-control function may have been neglected at one of the two test sites.

Overview of Telephone Follow-up Interview Protocol

The telephone follow-up interviews were conducted approximately 12 months after the initial call to the CIS. These interviews were conducted by four experienced tele-

Table 1. List of counterarguments provided by telephone counselors in response to specific barriers reported by CIS callers (Question: "What might prevent you from getting a mammogram?")

Checklist of barriers	Scripted counterarguments
Nothing would keep me from getting a mammogram	That's good to hear because getting a mammogram is very important to your health.
Cost	Your insurance may pay for mammograms. We can refer you to low-cost facilities.
Radiation	The radiation dose is extremely small; it's less than the radiation you would get in a dental x ray.
Pain	Very few women feel pain during a mammogram. Normally, there's little or no discomfort.
Physician never told me	Now that you know how important it is, you should ask your doctor for a mammogram. We can also give you the names of facilities that let you make your own appointment.
May find cancer	That's always a possibility. But with a mammogram, breast cancer can be found early, when treatment is most effective. The rate of cure is almost 100% when the cancer is found at a very early stage.
I don't know	What do you think might be the reason? I want to stress how important it is to get a mammogram, even if you have no symptoms. It takes only about 15 minutes and could save your life.
No symptoms	A mammogram can find breast cancer long before you have any symptoms that could be felt by you or your doctor. The earlier the cancer is found, the more likely it can be cured.
Too many other problems; inconvenient; too busy	I want to stress how important it is to get a mammogram, even if you have no symptoms. It takes only about 15 minutes and could save your life.

phone interviewers who were blinded to the intervention/control condition of respondents. The overall response rate was a highly respectable 87% ($n = 1831$).

The telephone follow-up interviews took about 10-12 minutes to complete and included questions on knowledge of screening-mammography guidelines, attitudes and beliefs about screening mammography, screening-mammography behavior (ever had screening mammogram, date and location of most recent screening mammogram), behavioral intentions with respect to screening mammography, and self-reported barriers that prevented the subject from getting a mammogram. Subjects were also asked whether a CIS counselor talked with them about screening mammography and whether they received a CIS mailout describing screening mammography. All subjects were asked whether they thought proactive counseling by the CIS was appropriate and should be continued as a service to the public. At the completion of the follow-up interview, all incorrect answers to the knowledge questions were briefly discussed and corrected by the interviewers, and, as noted previously, all nonadherent callers (both intervention and control) were encouraged to obtain a mammogram.

Self-reported Screening Mammography

The major outcome measure in this study is self-reported screening mammography, which appears to be both a valid and reliable indicator of actual mammography usage (12). During the 12-month follow-up interviews, subjects were asked a series of questions designed to assess their current screening-mammography behavior. These data were subsequently coded as to whether the subject was currently adherent (at the time of the follow-up interview) to NCI-recommended guidelines for screening mammography; the guideline for women 40-49 years of age is every 1-2 years and for women 50+ years of age is every year. The major research hypothesis is that adherence to these guidelines will be higher among women exposed to the SMCP.

RESULTS

Sample Description

Table 2 reports the sociodemographic and related characteristics of the sample. As shown, the vast majority of

Table 2. Characteristics of sample by experimental condition and test site

Characteristic	Total sample*		Intervention		Control		<i>P</i> value (chi-square)	Site A		Site B		<i>P</i> value (chi-square)
	N	%	N	%	N	%		N	%	N	%	
Age, y												
40-49	659	36.9	311	36.5	348	37.3	NS†	520	36.6	139	38.3	NS
50-59	443	24.8	206	24.2	237	25.4		348	24.5	95	26.2	
60+	683	38.3	335	39.3	348	37.3		554	38.9	129	35.5	
Education												
Grade school	26	1.5	12	1.4	14	1.6	NS	23	1.6	3	0.9	NS
Some high school	66	3.8	37	4.5	29	3.2		53	3.8	13	3.8	
High-school graduate	457	26.4	222	26.7	235	26.1		353	25.3	104	30.8	
Some college	612	35.3	299	35.9	313	34.7		495	35.5	117	34.6	
College graduate+	572	33.0	262	31.5	310	34.4		471	33.8	101	29.9	
Income												
<\$20 000	405	24.4	194	24.7	211	24.2	NS	315	24.0	90	25.8	NS
\$20 000-29 999	290	17.5	135	17.2	155	17.8		223	17.0	67	19.2	
\$30 000-39 999	269	16.2	132	16.8	137	15.7		215	16.4	54	15.5	
\$40 000-49 999	214	12.9	103	13.1	111	12.7		167	12.8	47	13.5	
\$50 000+	481	29.0	222	28.2	259	29.7		390	29.8	91	26.0	
Race/ethnicity												
White	1561	90.0	751	90.7	810	89.3	NS	1253	90.0	308	90.3	NS
Other	174	10.0	77	9.3	97	10.7		141	10.0	33	9.7	
Caller type												
Friend/relative of cancer patient	1015	56.7	472	55.3	543	58.0	NS	799	56.1	216	58.9	NS
General public/other	776	43.3	382	44.7	394	42.0		625	43.9	151	41.1	
Intervention versus control												
Intervention	870	47.5	—	—	—	—	—	698	48.0	172	45.5	NS
Control	961	52.5	—	—	—	—	—	755	52.0	206	54.5	

*Data reported in Table 2 were obtained from the CIS CRFs and the baseline survey appended to the CRFs (*n* = 1831). Variations in sample size are due to item nonresponse/missing data, which is highest for total family income (approximately 9%). Missing data typically ranges from 2% to 3%.

†NS = not significant.

callers were White/Anglo (90%), with at least a high-school education (95%). This profile conforms to that of CIS callers in general (13). In addition, approximately 57% were friends or relatives of cancer patients. Also of note is that the characteristics of the sample did not differ by experimental condition or by test site.

Based on historical CRF data, both sites should have accrued approximately the same number of subjects. As shown in Table 2, however, site A actually enrolled 79% of the total sample (*n* = 1453 of 1831). It is important to note in this regard that the contiguous geographic service areas of site A and site B were subsequently combined into one service area by the NCI as part of the CIS contract renewal process, which unfortunately occurred during the accrual period of the CCSR study. This resulted in site A and site B competing with one another for the same service area. Site A was eventually awarded the CIS contract, with site B terminating its service with several months remaining during the accrual period of the CCSR study.

Site A was also the principal applicant organization for the CCSR study, with site B serving as a subcontractor to site A. Given these extenuating circumstances, the analyses reported below will examine differences by site.

Process Evaluation

Several questions were included in the follow-up interviews to provide opportunities for process evaluation. Three questions had to do with exposure to key elements of the SMCP. As indicated in Table 3, intervention subjects were much more likely to report receiving screening-mammography counseling from the CIS; they were much more likely to report receiving print material in the mail concerning screening mammography; and they were more likely to have heard about recent legislation involving reimbursement for screening mammography. All of these differences, which target core elements of the SMCP, had high statistical significance.

Table 3. Overview of findings from process evaluation

12 months' follow-up survey*	Intervention		Control		<i>P</i> value (chi-square)
	N	%	N	%	
Was screening mammography discussed by CIS telephone counselor?					
Yes	539	62.2	77	8.0	< .001
No/not sure	328	37.8	881	92.0	
Did caller receive mailed material describing screening mammography?					
Yes	561	64.8	215	22.4	< .001
No/not sure	305	35.2	745	77.6	
Heard of any special insurance laws about screening mammography?					
Yes	208	24.1	134	14.0	< .001
No/not sure	654	75.9	824	86.0	
Should CIS continue to make screening mammography recommendations even if this information is not requested by caller?					
Yes	790	91.4	847	88.1	.02
No/not sure	74	8.6	114	11.9	
Caller requested additional screening mammography materials?					
Yes	409	47.6	624	65.2	< .001
No	450	52.4	333	34.8	

*n = 1831. Slight variations in sample size due to missing data/item nonresponse.

Another indication of the strength of the experimental manipulation is whether intervention and control subjects differed in their requests for more information about screening mammography at the end of the study. If the SMCP worked according to plan, intervention subjects should request less information at the end of the study than control subjects. As shown in Table 3, this is precisely what was found, with 65% of the control subjects requesting such information at 12 months' follow-up compared with 48% of the intervention subjects.

Finally, a question included in the follow-up survey asked callers whether they thought proactive counseling for screening mammography should be continued by the CIS. Overwhelming endorsement for this policy was reported by CIS callers, with 90% responding that proactive counseling should be provided by the CIS.

The intervention versus control differences shown in Table 3 were, for the most part, replicated within each intervention site. Two exceptions to this pattern were the following: 1) when the sample was stratified by site, intervention and control subjects at both sites did not differ statistically in their endorsement of proactive counseling for screening mammography (i.e., intervention and control subjects at both sites were overwhelmingly supportive of proactive counseling) and 2) only within site A was there a significant difference between intervention and

control subjects in their request for additional information at the end of the study (i.e., site A: intervention = 45.9%, control = 67.2%, $P < .001$; site B: intervention = 56.1%, control = 58.0%, P = not significant).

Another dimension of process evaluation is whether the intervention affected the precursors to behavior change that presumably link the experimental manipulation to the outcome. Within the context of this study, two such intermediate markers include knowledge of screening-mammography guidelines and the perceived efficacy of screening mammography and early diagnosis. If the SMCP was successful in conveying this information to callers, then subjects assigned to the intervention group should score higher on these dimensions at 12 months' follow-up than subjects assigned to the control group. As shown in Table 4, there was a modest, but statistically significant, difference in knowledge of screening-mammography guidelines for women 50+ years of age (in the predicted direction). No such difference was found with respect to knowledge of screening-mammography guidelines for women 40-49. The vast majority of incorrect answers to the knowledge question about women 40-49 years of age occurred because subjects incorrectly identified "every year" as the recommended guideline for screening. With respect to the two efficacy items (i.e., efficacy of screening mammography for early detection of

Table 4. Differences in screening mammography knowledge and beliefs by intervention condition

	Intervention		Control		P value (chi-square)
	N	%	N	%	
12 months' follow-up survey*					
Knowledge of guidelines: 40-49 y					
Correct	315	36.0	323	33.5	NS†
Incorrect	560	64.0	642	66.5	
Knowledge of guidelines: 50+ y					
Correct	657	75.0	684	70.7	< .04
Incorrect	219	25.0	284	29.3	
Belief in efficacy of screening mammography to find breast cancer early					
Very high	501	58.0	536	56.0	NS
High	240	27.8	263	27.4	
Not high	123	14.2	159	16.6	
Belief in efficacy of early diagnosis to increase chances of cure					
Very high	526	61.0	559	58.9	NS
High	229	26.5	278	29.3	
Not high	108	12.5	112	11.8	

*n = 1831. Slight variations in sample size due to missing data/item nonresponse.

†NS = not significant.

breast cancer and efficacy of early detection with respect to cure), a pronounced ceiling effect was encountered. Female CIS callers already appear to believe in the efficacy of screening mammography and early detection, as evidenced by the exceptionally high scores found in the control group (i.e., 85%-90% of control subjects rated these two dimensions of efficacy as "very high" or "high," thus leaving little or no room for improvement by the SMCP).

Outcome Evaluation

Overall, nearly 64% of the subjects (1163 of 1831) were classified as adherent with NCI guidelines at 12 months' follow-up. Preliminary analyses indicated no differences between the intervention and control groups (intervention = 65.2%, control = 63.3%; P = not significant). This finding of no difference prompted additional exploratory analyses using logistic regression. Several different models were examined during this exploratory phase, consisting of various combinations of caller age, education, type of caller, total family income, site, and intervention versus control condition. Emerging from these exploratory analyses was a significant three-way interaction involving intervention/control condition, income, and site. The detection of this interaction thus required that all subsequent analyses be stratified by site and income. The results of this stratification can be summarized as follows: Within site B there was no relationship between intervention condition and adherence, even when stratified by income (i.e., <\$30 000 versus \geq \$30 000); however, within site A such a relationship was found. As shown in Table 5, among callers reporting a total family income of \$30 000 or more, the SMCP was significantly related to screening-mammography adherence in the predicted direction, with an odds ratio of 1.38. Also shown in Table 5 is a significant

inverse relationship (at site A) between caller age and adherence to screening-mammography guidelines. This same inverse relationship was also found within site B using the same set of predictor variables presented in Table 5 (odds ratio = 0.97; P = .055).

To further explicate this finding of a significant intervention effect at site A, we calculated the probability of being currently adherent to screening-mammography guidelines separately by intervention condition. For example, the probability of being adherent for a woman from the general public, 60 years of age, with a high-school education, and in the intervention group was calculated using $1/[1 + \exp [-(\text{intercept} + \text{intervention} + \{60 \times \text{age}\} + \{3 \times \text{education}\})]] = 1/[1 + \exp [-(1.9367 + 0.3220 + \{60 (-0.0231)\} + \{3 (0.0264)\})]] = 72.15\%$. (Caller-type = 0 for general public, which is why this regression coefficient was not included in the calculation.) In contrast, the probability of being adherent for a woman of the same age, caller type, and education who was in the control group was calculated using $1/[1 + \exp [-(\text{intercept} + \{60 \times \text{age}\} + \{3 \times \text{education}\})]] = 1/[1 + \exp [-(1.9367 + \{60 (-0.0231)\} + \{3 (0.0264)\})]] = 65.25\%$. This same general strategy can, of course, be used to calculate the probability that any given individual with a specific set of characteristics (included in the prediction equation) will be currently adherent to screening mammography guidelines. Using the above-derived probabilities, it can be shown that this 7-percentage-point difference (i.e., 72.15% versus 65.25%) does indeed reflect the 1.38 odds ratio reported in Table 5. Thus:

$$\frac{0.7215/(1-0.7215)}{0.6525/(1-0.6525)} = 1.38$$

Based on the three-way interaction detected in this analysis, it would appear that the SMCP was *not* effective in

Table 5. Logistic regression analysis of screening mammography among CIS callers with $\geq \$30\ 000$ total family income—site A

Predictor variable*	Adherence to guidelines at 12 months' follow-up		
	Parameter estimate	Odds ratio	Confidence interval
Intervention versus control	0.322	1.38	(1.01–1.89)†
Age	–0.023	0.98	(0.96–0.99)‡
Education	0.026	1.03	(0.88–1.20)
Caller type	–0.045	0.96	(0.69–1.33)

*n = 783. Chi-square for model = 13.46, *df* = 4, *P* = .009. Age coded as continuous variable; all others coded as categorical variables. Missing values for income and education were substituted by their corresponding mean values. A categorical value for income, \$30 000–\$39 000, was assigned to 170 subjects who had missing data on income. Similarly, the mean categorical value for education (i.e., some college) was used to replace missing data for 103 subjects.

†*P* = .04.

‡*P* = .003.

overcoming economic barriers to screening mammography, as evidenced by the inability of the SMCP to affect the behavior of callers reporting less than \$30 000 income. Less apparent is why the SMCP had a positive effect only at site A. This question prompted additional analyses comparing the intervention subjects at both sites with respect to their self-reported exposure to the intervention. If the

intervention was implemented with equal success at both sites, there should be no differences in these measures. As shown in Table 6, however, intervention subjects at site A were significantly more likely to report receiving telephone counseling (*P* < .001) and significantly less likely to request information about screening mammography at the end of the study (*P* < .02) than intervention subjects at site B.

Finally, callers who were nonadherent at the follow-up interviews were asked to indicate the factors which prevented them from obtaining a screening mammogram. As shown in Table 7, the most frequently cited barrier was inconvenience or being too busy (52%), which far surpassed other traditional barriers such as cost (36%) and lack of a physician referral or recommendation (34%). Being in good health/having no symptoms (34%) and fear of radiation (29%) also ranked high as barriers to screening mammography, but fear of pain (8%), finding breast cancer (11%), and embarrassment (4%) ranked much lower in frequency.

A comparison of intervention versus control subjects revealed no differences in the reporting of such barriers as cost, fear of radiation, fear of finding breast cancer, lack of physician referral, fear of pain, fear of embarrassment, or lack of perceived need (i.e., no symptoms/in good health). Intervention subjects were significantly less likely, however, to report inconvenience or a busy schedule as barriers to screening mammography than were control subjects (Table 7). Interestingly, this same difference (i.e., with respect to inconvenience/being too busy) was replicated within site A but *not* within site B (site A: intervention = 46.2%, control = 57.3%, *P* = .03; site B: intervention = 46.7%, control = 53.0%, *P* = not significant).

Table 6. Self-reported exposure to the SMCP among intervention subjects at both sites

12 months' follow-up survey*	Intervention subjects				<i>P</i> value (chi-square)
	Site A		Site B		
	N	%	N	%	
Was screening mammography discussed by CIS telephone counselor?					
Yes	447	65.1	86	50.0	< .001
No/not sure	240	34.9	86	50.0	
Did caller receive mailed material describ- ing screening mammography?					
Yes	454	66.1	102	59.6	NS†
No/not sure	233	33.9	69	40.4	
Heard of any special insurance laws about screening mammography?					
Yes	164	24.1	41	23.8	NS
No/not sure	518	75.9	131	76.2	
Caller requested additional screening mammography materials?					
Yes	312	45.9	96	56.1	< .02
No	368	54.1	75	16.9	

*Data reported in Table 6 are restricted to intervention subjects at both sites (n = 870). Slight variations in sample size due to missing data/item nonresponse.

†NS = not significant.

Table 7. Self-reported reasons for not obtaining a screening mammogram at 12 months' follow-up

Reason for nonadherence*	Total sample		Intervention		Control		<i>P</i> value (chi-square)
	N	%	N	%	N	%	
Cost	188	36.2	84	35.9	104	36.5	NS†
Fear of radiation	152	29.3	67	28.6	85	29.9	NS
Pain	41	7.9	19	8.1	22	7.7	NS
Physician never told me	175	34.0	80	34.5	95	33.6	NS
Might find cancer	58	11.2	25	10.8	33	11.6	NS
No symptoms/good health	171	33.9	77	34.4	94	33.6	NS
Too busy/inconvenient	268	51.8	108	46.3	160	56.3	.02
Embarrassment	22	4.3	9	3.9	13	4.6	NS

*Responses were obtained from a checklist, with each item on the checklist coded as a separate question. Only those callers nonadherent to NCI guidelines (at 12 months' follow-up) were asked these questions. Callers who reported that they had an appointment that was pending also were not asked these questions. Sample size varies from 513 to 518, depending on the amount of missing data per item on the checklist.

†NS = not significant.

DISCUSSION

This study represents the first randomized trial of a proactive counseling protocol within the CIS. The results of this study are encouraging at several levels. From the perspective of CIS callers, it would appear that there is strong endorsement for proactive counseling of screening mammography. Thus, 90% of the CIS callers surveyed at 12 months' follow-up recommended that the CIS continue this practice. Similarly, debriefing sessions with CIS telephone counselors provided equally positive evaluations of the proactive counseling protocol, which took about 6 minutes to complete.

Questions asked during the follow-up interviews suggest that the SMCP did, in fact, expose intervention subjects to substantially higher levels of information and counseling about screening mammography. For example, intervention subjects were much more likely than control subjects to report receiving both telephone counseling and mailout material describing screening mammography. Additional evidence supporting the saliency of the experimental manipulation comes from a question asking callers (at 12 months' follow-up) if they would like more information about screening mammography. If the SMCP was successful in increasing the amount of information provided to intervention subjects, then requests for such information at the end of the study should be higher in the control group. Such a difference was found: 65% of the control subjects requested more information, compared with 48% of the intervention subjects.

With respect to self-reported screening mammography, nearly 64% of CIS callers enrolled in the study were classified as adherent to NCI guidelines at 12 months' follow-up. A significant intervention effect for the SMCP was found but only at site A and only among CIS callers with total family income of \$30 000 or more. As noted previously, there was evidence to suggest that the SMCP may have been implemented more successfully at site A.

This conclusion is based on such markers as subject accrual (significantly lower at site B), less frequent reports of receiving key elements of the SMCP by intervention subjects at site B (e.g., telephone counseling related to screening mammography), and more frequent requests by intervention subjects at site B for additional information at the end of the study.

Given that the proactive counseling protocol was effective only among callers with incomes of \$30 000 or more, it would appear that the counseling intervention was not effective in overcoming known economic barriers to screening mammography (5,6,8,9,14-16). In anticipation of this problem, the SMCP included specific referrals to low-cost facilities. It would seem, however, that this component of the intervention needs to be strengthened. At the time this study was conducted, the number of truly low-cost screening mammography facilities was limited. Efforts to use the CIS to promote low-cost mammography services supported through the Breast and Cervical Cancer Mortality Prevention Act of 1990 would seem to offer additional opportunities in this regard that were not available when this study was conducted. In addition, the reinforcement mailout to CIS callers might specifically mention the low-cost facilities that operate in the caller's area, which would augment the more generic material that was mailed to callers in this study.

Additional evidence suggesting the need to strengthen the reinforcement mailout comes from the question asking subjects (at 12 months' follow-up) whether they would like more information about screening mammography. Although control subjects, as noted above, were significantly more likely to request such information, nearly 50% of the intervention subjects also made this request, in spite of their previous exposure to the SMCP.

The findings from this study also have implications for behavioral science theory. The presumed impact of the SMCP cannot be attributed to such factors as increased knowledge or more positive beliefs about the efficacy of

screening mammography. The SMCP had only a modest impact on knowledge, and women calling the CIS (who were eligible for this study) appeared to believe already in the efficacy of screening mammography and early detection. Instead, it would seem that factors traditionally conceptualized as barriers to health care may be key. For example, economic barriers emerge as a major factor, as evidenced by the inability of the SMCP to increase adherence among women with incomes of less than \$30 000. Similarly, perceptions of screening mammography being inconvenient or not easily accommodated within a busy schedule were reported significantly more often by nonadherent control subjects than by nonadherent intervention subjects. Cost as a barrier to screening mammography is well known and frequently cited in the literature. Among middle class, White/Anglo females (i.e., the typical user of the CIS), however, one of the more important barriers may simply be inconvenience or being too busy, which is a cognitive barrier that may be amenable to change by counseling interventions such as the SMCP (e.g., providing motivational messages to overcome perceptions of inconvenience/being too busy).

SUMMARY

The proactive counseling protocol tested in this study was found to be effective among a subgroup of CIS callers (with total family income \geq \$30 000) that constitutes nearly 60% of all age-eligible female callers to the CIS. With respect to this population subgroup, there would appear to be sufficient evidence to merit dissemination research to examine the diffusion and exportability of the SMCP within the CIS. The fact that the SMCP was found to be successful in only one of the two test sites serves to underscore the need for such research. With respect to economically disadvantaged CIS callers, however, additional efficacy trials should be encouraged. Because a 6-minute protocol over the telephone is probably the maximum that can be allocated to proactive counseling within the CIS, such efforts might focus on strengthening the reinforcement mailout for low-income populations (e.g., providing personalized written feedback and reinforcement from the counseling session, using low-literacy and culturally sensitive print material to supplement or replace generic material). At the same time, expectations must be tempered by recognizing the limitations of a brief telephone counseling protocol and mailout, especially with respect to overcoming profound structural barriers such as socioeconomic status and the cost of health care in this country. Fortunately, we are at a point in time when the CIS can proactively promote low- or no-cost screening-mammography services that are supported by the Breast and Cervical Cancer Mortality Prevention Act of 1990. This fortuitous circumstance highlights the timeliness of implementing a proactive counseling protocol for breast-cancer screening within the national CIS network.

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Role of the Cancer Information Service in a National Education Initiative on Cancer Clinical Trials

Katherine Crosson, Rosemarie Slevin, Julie Keany*

Although the participation of cancer patients in clinical trials is critical to the identification of new treatment protocols that improve survival or reduce treatment side effects, usually fewer than 3% of all newly diagnosed patients are enrolled in clinical trials. The ability to recruit more of these patients to clinical trials would increase the number of studies that could be done and would move promising new treatments more quickly into routine practice. This paper examines the role that the Cancer Information Service (CIS) played in the nationwide education initiative sponsored by the National Cancer Institute to increase accrual to clinical trials. Efforts to increase patient and public awareness of clinical trials as a treatment option are described, and the unique role of the CIS in response to the education initiative is highlighted. The effect of the initiative on accrual is discussed, and recommendations for additional studies are provided. [Monogr Natl Cancer Inst 14:131-137, 1993]

BACKGROUND

In the early 1980s, National Cancer Institute (NCI) recruitment efforts focused on community-based centers, where most cancer patients are treated. Specifically, through its Community Clinical Oncology Program (CCOP), NCI sought to bring the research of cancer centers from major academic and research institutions into the community by encouraging the involvement of community physicians in clinical trials research (1). These efforts affected accrual to clinical trials dramatically. Since 1981, more than 50% of all patients in clinical trials have been referred by community oncologists (1), but despite these efforts, participation levels remain below those desired. Usually, fewer than 3% of all newly diagnosed patients are enrolled in clinical trials (3).

In 1988, in response to increasing concern about the slow recruitment of patients to NCI-supported clinical trials, NCI's Division of Cancer Treatment set a goal of doubling the number of patients entering clinical trials by 1992. Research study groups examined methods to encourage greater participation by physicians, and NCI developed streamlined processes for entering and following patients during trials. In addition to these activities, NCI recognized that increasing the public's awareness about clinical trials was critical to the achievement of its goal. Research about accrual to clinical trials revealed that patients who are eligible to participate in trials often refuse

because of concerns about experimentation, toxic side effects, and costs (1).

EDUCATIONAL EFFORTS

NCI developed an educational initiative, "Patients Helping Progress: Cancer Clinical Trials and You," to reach the public, patients and their family members, and health professionals with the clinical trials message. This initiative mixed traditional avenues for patient-education programs with mass-media and communication strategies. Initial promotion efforts included the following:

- Addition of a statement about clinical trials in all NCI patient-education publications.
- Development of a fact sheet about clinical trials for a patient audience.
- Use of national television and radio news and talk shows and the popular press to increase accrual.
- Use of local media to advertise clinical trials and recruit clinical trial investigators.

In 1988, NCI began the process of incorporating a statement about clinical trials as a treatment option in all appropriate publications, as they were developed or revised. In addition, the patient education fact sheet "Cancer Treatment: Consider the Possibilities" was completed in 1989. The distribution plan for the fact sheet included placing announcements about the availability of the publication and referring readers to the Cancer Information Service (CIS) for information relating to specific trials.

Additionally, an article-placement plan targeting the popular press and local newspapers was developed. A series of standard articles and story angles was developed for use by the print media. Announcements about study results, popular with the media, were used by the NCI Press Office as opportunities to promote clinical trials as a treatment option. In addition, NCI used the "Hometown News Release" format. These press releases highlighted the participation of local physicians and hospitals in NCI-supported studies and let the public know that cancer patients could receive treatment close to home. Medical and health reporters received targeted mailings and follow-up telephone calls to encourage their use of the materials and messages about clinical trials.

*See "Notes" section following "References."

INVOLVEMENT OF THE CIS

To enable the public to identify available clinical trials, each promotion effort has included the CIS toll-free number (1-800-4-CANCER) as a source for more information. NCI recognized the CIS as an essential vehicle for responding to calls generated by the promotion efforts on clinical trials and for educating the public about state-of-the-art cancer treatment.

To prepare the CIS staff to respond to inquiries about clinical trials, NCI proposed the development of a comprehensive training program. Involvement of the CIS staff members in developing the training program was critical. Their participation helped NCI explore potential biases that affected the manner in which the CIS information specialists discussed clinical trials with callers. Furthermore, the CIS staff members recognized their ability to identify patients potentially eligible for clinical trials from the general population of callers. This knowledge formed the basis for the development of a counseling framework that enables CIS staff to discuss clinical trials as a treatment option even when callers do not specifically request the information.

NCI identified potential staff biases about clinical trials and determined the most common and most difficult questions they received about clinical trials. Responses revealed wide variations in attitudes and perceptions about clinical trials among the staff. Some staff members believed that participation in clinical trials was appropriate only when all other treatment options had failed; others were more likely to urge callers to consider participation without fully discussing the potential disadvantages of participation. In addition, staff members expressed concerns about their inadequacy to answer questions about topics such as randomization, eligibility, cost reimbursement, and study results. They also expressed concern about the lack of printed educational materials to help explain clinical trials.

The training program that resulted, "Counseling Callers About Clinical Trials," was designed to provide the CIS information specialists with a sufficient knowledge base to explain clinical trials, to identify when to introduce clinical trials as a treatment option, and to discuss objectively the potential advantages and disadvantages of participation. The training package includes a "Leader's Guide" that provides a step-by-step approach to teaching about clinical trials. This approach is covered in six learning modules. Each module contains objectives, content, suggested teaching methodology, and audiovisual aids. The guide is designed to provide an interesting, interactive learning experience. Each participant receives a workbook that contains information about clinical trials, a self-assessment test, a discussion of responses, a list of difficult questions, and an "answer sheet" and exercises. The guide also includes fact sheets about specific topics such as the advantages and disadvantages of participation in clinical trials. Fact sheets can be sent to the caller to reinforce information provided by the information specialist.

In addition to presenting general information about clinical trials, study design, and Physician Data Query (PDQ), an NCI database that includes information on supported and approved clinical trials, the training program gives the information specialists the opportunity to discuss their feelings, identify their biases about clinical trials, and role-play different counseling strategies for callers. One of the most valuable components of the training program is the structural framework provided for counseling callers about cancer treatment and, more specifically, about clinical trials as a treatment option. This counseling framework, included at the request of the CIS staff, is based on a previous CIS training program on smoking cessation that used the Prochaska model of precontemplation, contemplation, action, maintenance, and relapse for predicting change in smoking status for self-changers (2). This model was adapted for the clinical trials training program.

The "Counselor Response Model" includes the four stages that form a continuum through which the CIS information specialist guides callers who request information on clinical trials (Table 1). The goal is to provide callers at each stage of the decision-making process with the information they need to make a decision about considering clinical trials as a treatment option. The model helps the information specialist determine when and if the option of clinical trials should be introduced to the caller. Specifically, the counseling suggestions included in the model help the information specialist determine when to use PDQ to identify standard treatment options for a particular type and stage of disease. If PDQ indicates that the treatment options include both standard and investigational treatments, the information specialist can introduce clinical trials as a treatment option.

Before the development of the training program, callers were not routinely provided information on clinical trials unless they specifically requested such information. Thus, the training program increases the number of callers who receive clinical trials information. The Counselor Response Model also provides the information specialist with tips about issues such as the informed consent process, advantages and disadvantages of participation, and costs and insurance coverage. Although the model provides a framework for the calls, it does not replace the normal dynamics of the counselor and caller interchange.

RESULTS

By 1990, more than 20 NCI publications included a standard statement on clinical trials. That statement continues to be incorporated routinely in new publications. More than 100 000 copies of "Cancer Treatment: Consider the Possibilities," a publication targeting patients, were distributed. In addition, distribution of NCI's centerpiece publication, "What Are Clinical Trials All About?" increased following the education initiative. Davis et al. (3) discuss this booklet elsewhere in this monograph. (See Figs. 1 and 2.)

Table 1. Counseling callers about clinical trials: A training program for the Cancer Information Service (Counselor Response Model)

Step 1: Precontemplation	⇨	Step 2: Contemplation	⇨	Step 3: Action	⇨	Step 4: Maintenance
Caller is seeking general information on treatment options. Caller does not indicate any knowledge of clinical trials.		Caller indicates an interest in obtaining more information on participating in clinical trials.		Caller has made the decision to investigate available clinical trials.		Caller has made a decision to participate or not participate in a clinical trial.
Goal: To introduce clinical trials as a treatment option, when appropriate.		Goal: Enable caller to investigate clinical trials as a treatment option.		Goal: Enable caller to make an informed decision about participation in a clinical trial.		Goal: Enable caller to remain an active participant in decision making about treatment.
Information needed from caller: Is there a diagnosed patient? Initial diagnosis or recurrence? What type of cancer? What is stage of disease? Does PDQ statement list clinical trials as an option?		Information needed from caller: Confirm that clinical trials are a treatment option. Does <i>patient</i> wish to participate in a clinical trial? What is physical status of patient? Is the patient receiving treatment now?		Information needed from caller: If diagnosed patient, confirm information needed to conduct a PDQ search. If not diagnosed patient, provide counseling suggestions for precontemplation stage.		Information needed from caller: What are caller's concerns about the decision? Has he or she discussed concerns with physician and others?
Counseling suggestions to give: Introduce clinical trials as a treatment option. Define clinical trials. Encourage caller to discuss clinical trials with physician. Offer to send site-specific information and clinical trials booklet.		Counseling suggestions to give: Define clinical trials. Review advantages and disadvantages of clinical trials. Encourage patient to discuss clinical trials with physician. Explain PDQ database. Introduce availability of a PDQ search. Offer to send site-specific information and clinical trials booklet.		Counseling suggestions to give: Explain PDQ database. Explain phases of trials. Review questions to ask about clinical trial. Discuss informed consent. Discuss cost. Conduct a PDQ search if requested. Offer to send site-specific information and clinical trials booklet.		Counseling suggestions to give: Review treatment options. Review decision made and reasons why. Review pros and cons of decision as perceived by caller. Encourage caller to talk to physician. Conduct a PDQ search if appropriate. Suggest referrals for support. Suggest referrals for second opinion, hospice, home care, rehabilitation. Offer to send site-specific information and clinical trials booklet.

Use of the clinical trials message by newspapers and the popular press was significant. In 1989, more than 20 articles were placed in popular magazines and major newspapers. *Reader's Digest*, *Ladies Home Journal*, and the *New York Times Magazine* all featured articles about clinical trials and NCI's education initiative. Major daily newspapers, including *The Wall Street Journal* and *USA Today*, also carried stories on clinical trials.

The impact of these education efforts on the CIS call volume was dramatic. Fig. 3 illustrates the number of CIS inquiries about clinical trials from 1983 to 1990. Inquiries have risen steadily since 1983, with the first significant increases reflected in 1985 and 1986, when PDQ came into use. The effects of the education initiatives that began in late 1988 are obvious, however. Inquiries about clinical trials increased 63% in 1989. In 1990, the number of calls remained high despite an overall decrease in CIS call vol-

ume. Data from 1991 reflect a continued escalation of inquiries on clinical trials: the volume increased to more than 44 000 calls. (See Fig. 3.)

Fig. 4 demonstrates the direct correlation between the increases in call volume and the articles that appeared in newspapers and the popular press. In addition, whenever possible, the CIS tracked responses to specific promotion activities. Fig. 5 illustrates the increases in clinical trials inquiries from 1988 to 1990 resulting from newspaper and magazine coverage and the distribution of educational brochures. In addition, callers referred to the CIS by family, friends, and health professionals also increased. This increase may indirectly reflect the success of the education efforts. (See Figs. 4 and 5.)

The success of the initial education efforts is dwarfed only by the impact of the CIS training program. The training program was pretested with CIS senior staff in

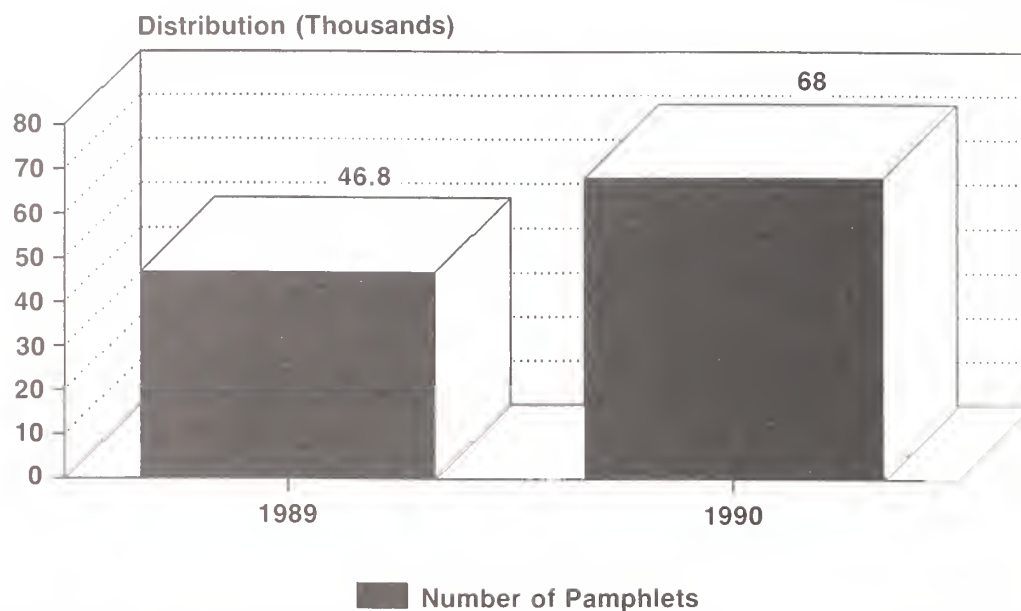


Fig. 1. "Cancer Treatment: Consider the Possibilities" pamphlet. Distribution began in 1989.

October 1988 and fully implemented across the country in early 1989. The overall response was very positive. The training program was comprehensive and innovative; the staff became more comfortable in answering even the most difficult clinical trials questions. Furthermore, the program was so well received that some CIS offices were

asked to train nurses and other health professionals at their parent institutions so that they could better discuss clinical trials with their patients.

Although the effectiveness of the training program in preparing the CIS staff to respond accurately to inquiries about clinical trials was expected, the tremendous effect of

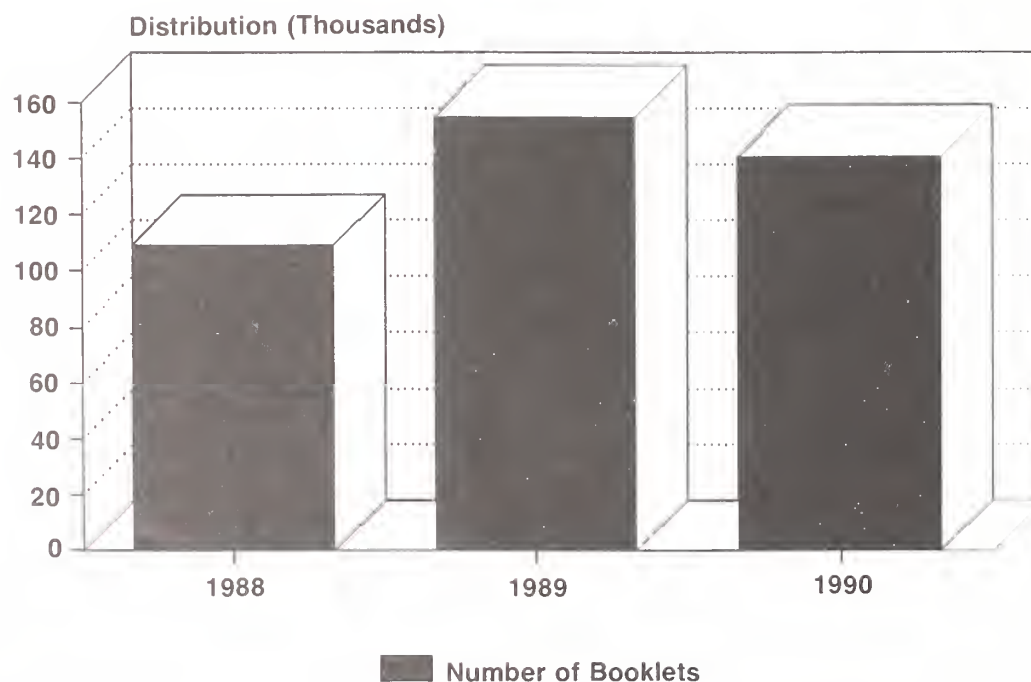


Fig. 2. "What Are Clinical Trials All About?" brochure.

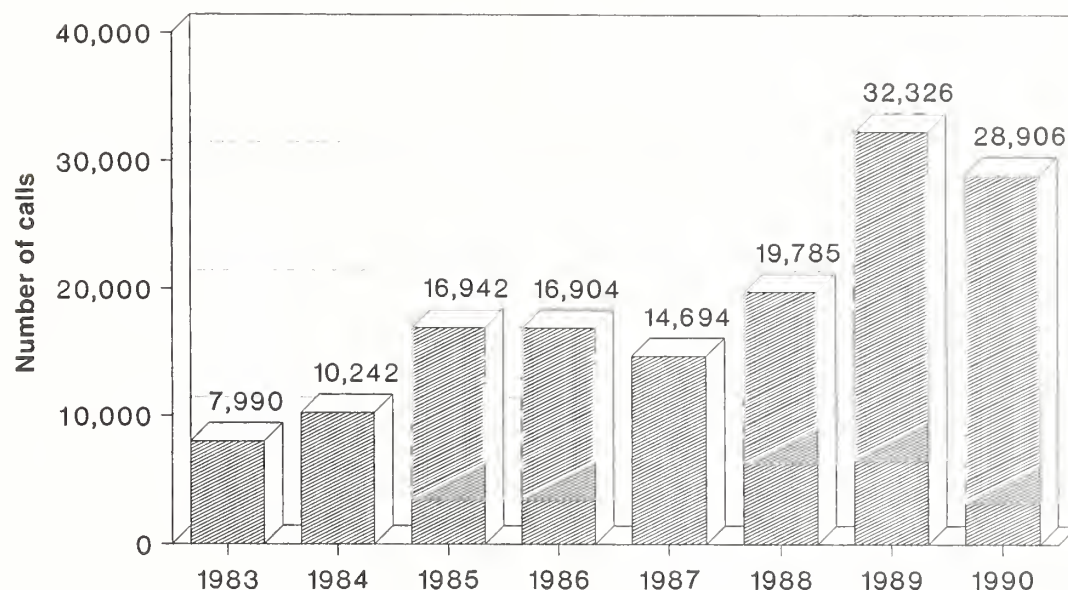


Fig. 3. Inquiries to the CIS on clinical trials.

adapting the Counselor Response Model to cancer-treatment questions was not anticipated. Anderson et al. (4) first reported the overwhelming effect of the Counselor Response Model on the frequency with which CIS staff initiated the discussion of clinical trials as a treatment option; they reported a 270% increase in the number of callers receiving information about clinical trials (4).

These were callers who did not request the information but who were identified by CIS staff as potentially eligible for clinical trials based on the information provided by PDQ. In the first year following the training, the CIS staff recommended the option of clinical trials more often than they responded to direct inquiries on clinical trials. The use of the investigational protocol file in PDQ increased

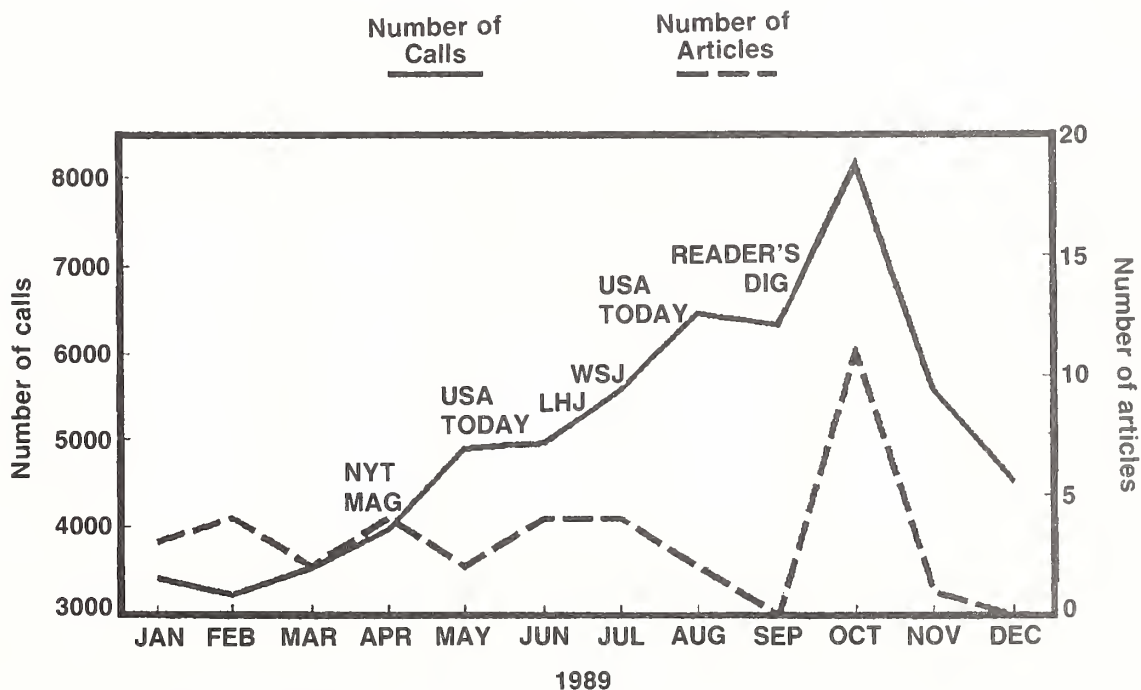


Fig. 4. CIS calls concerning clinical trials compared with the number of articles about the subject. NYT MAG = *New York Times Magazine*; LHJ = *Ladies Home Journal*; WSJ = *The Wall Street Journal*.

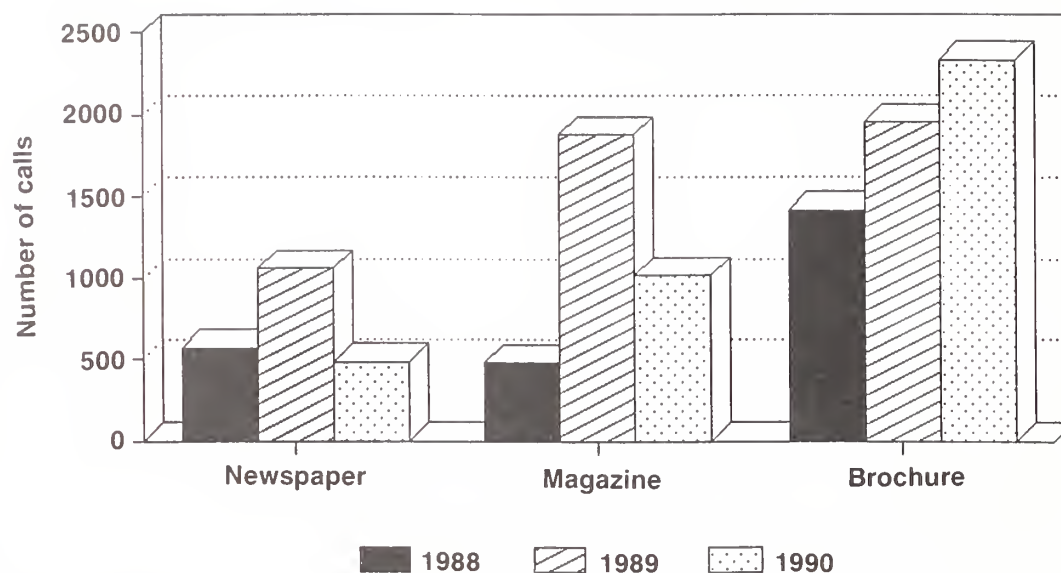


Fig. 5. Effect of education efforts on the number of calls received by the Cancer Information Service.

by 106% from 1988 to 1989, with more than 17 000 protocol searches conducted for callers. The number of searches remains high, with more than 16 000 searches conducted in 1990 and more than 24 000 in 1991. Additionally, referrals to NCI cancer centers and trials increased from 39 000 in 1986 to a high of 96 000 in 1989 and dropped to 95 000 in 1990. (See Fig. 6.)

DISCUSSION

Since 1988, accrual to NCI-supported, high-priority clinical trials increased. The greatest success has been in recruitment of patients to clinical trials involving colorectal, breast, and lung cancers. The success in recruiting patients to these trials has opened the door for more trials targeting other cancer sites.

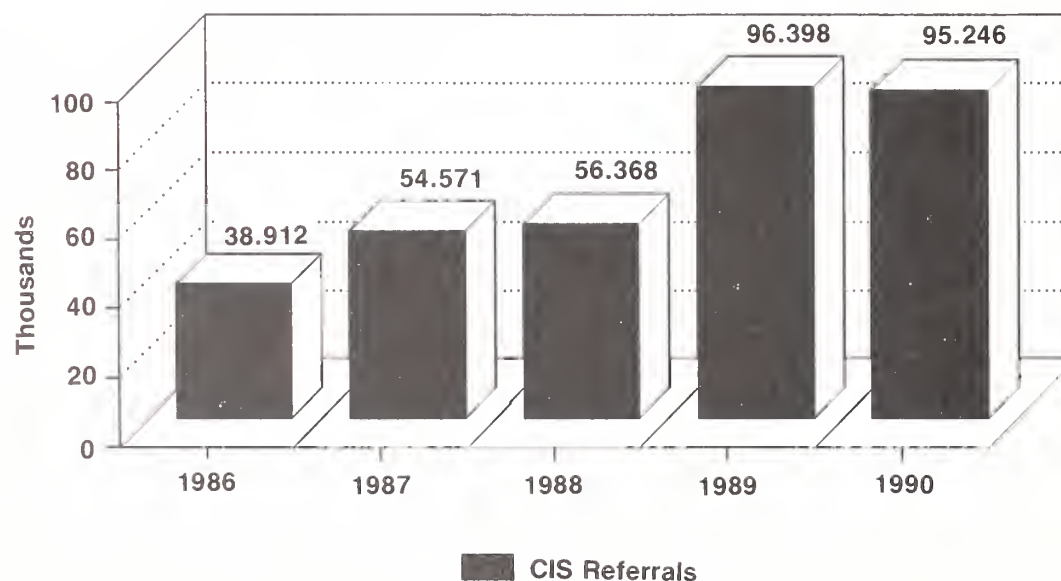


Fig. 6. Referral to National Cancer Institute centers and clinical trials. (Cancer Information Service data, 1986-1990.)

The success of the initial education efforts of incorporating a new message in standard NCI materials, while developing only a few well-targeted new publications, demonstrates the importance and cost-effectiveness of identifying existing media for new messages. Additionally, the success of the efforts to supplement traditional patient education avenues with an appeal to the mass media broadens the opportunities to reach more people, particularly those outside well-established cancer treatment facilities.

The success of the CIS training program also is significant. It demonstrates the pivotal role for the CIS in future NCI educational initiatives. Use of the clinical trials training program model is appropriate for other NCI patient-education and health-promotion initiatives. More specifically, adaptation of the Counselor Response Model for those initiatives holds tremendous potential for reaching callers with important information that may be unrelated to their initial inquiry. In addition, the successful training of the CIS staff on such a complex issue demonstrates the role of the CIS in enhancing patients' understanding of information provided by their health-care team. Issues such as participation in clinical trials are clearly a topic traditionally and most appropriately addressed by a patient's health-care team. As this education initiative demonstrates, however, the CIS played a unique role in encouraging the patient to discuss clinical trials with his or her health-care team. The CIS facilitated that discussion by providing patients with information to share with their physicians and by helping them consider participation in a clinical trial. Finally, the usefulness of the clinical trials training program for health professionals at the CIS parent institutions, which are predominantly NCI comprehensive cancer centers, suggests an expanding role for the CIS in supporting patient-education activities beyond the confines of the telephone service. The potential role of CIS staff in supporting patient-education activities should be explored.

The data strongly suggest that the CIS played a direct role in the increase in accrual. Therefore additional studies following up on callers referred to clinical trials should be supported. These studies will help determine more conclusively the role of the CIS in helping patients explore and understand clinical trials as a treatment option.

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Evaluation of the National Cancer Institute's Clinical Trials Booklet

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Evaluating the impact of written materials is a means to enhance the effectiveness of patient education, yet few controlled studies of publications have been completed. In 1984, as a result of a needs assessment, the National Cancer Institute (NCI) developed and pretested the booklet "What Are Clinical Trials All About?" The booklet was designed to help cancer patients make informed decisions about participation in clinical trials, which are critical for improving cancer treatment. The booklet, which is currently available, has been used internationally as a model for communicating information on clinical trials. Since 1985, the booklet has been used by the Cancer Information Service (CIS) as an educational tool for answering questions from cancer patients about treatment and clinical trials. The CIS, which has traditionally assisted NCI in the development and testing of educational materials, was involved in the pretesting and particularly the posttesting of this booklet. The CIS regional offices at Fox Chase Cancer Center and Sylvester Comprehensive Cancer Center together with National Institutes of Health Clinical Center and North Memorial Medical Center conducted a posttest evaluation of the booklet's effectiveness for cancer patients. Two hospitals tested the booklet on patients who were eligible for a specific clinical trial, and two hospitals tested the booklet on patients who were theoretically eligible for a clinical trial (with a cancer site and stage for which a trial existed). Patients were randomly assigned: 203 experimental subjects received the booklet, and 194 control subjects were not given the booklet until after a 2-week posttest examining attitudes, knowledge, and beliefs about clinical trials. At the posttest, experimental group members were significantly more likely to feel somewhat or very clear in their understanding of clinical trials, and control group members were more likely to feel undecided or confused. Experimental group members were also significantly more knowledgeable about the voluntary nature of entering or leaving clinical trials and about where trials are conducted. Neither group assignment nor reading the booklet significantly increased the likelihood of participating in a clinical trial. Consistent with the booklet's objective, however, exposure to the booklet increased patients' knowledge and understanding of clinical trials, implying that informed decisions could be made. [Monogr Natl Cancer Inst 14:139-145, 1993]

INTRODUCTION

Cancer-treatment studies, also known as investigational protocols or clinical trials, are critical for improving can-

cer treatment. Cancer survival rates have greatly increased for many types of cancer as a result of the past three decades of clinical studies. More rapid accrual to clinical trials leads to faster completion of trials and, thus, to a more rapid pace of discovery.

The National Cancer Institute (NCI) has been working to increase accrual to clinical trials because when the rate of patient participation is low, many studies cannot be completed over a reasonable period of time. Fewer than 3% of new cancer patients in the United States take part in clinical trials (1).

There have been a number of barriers to patient accrual. Some researchers have cited overly restrictive eligibility requirements as a major barrier to accrual (2). Physicians have also been reluctant to enter their eligible patients in randomized clinical trials (3). Concern about changes in the doctor-patient relationship brought about by referral to the medical institutions where the trials take place have been cited as the major reason for this reluctance (4).

The difficulty of presenting the informed consent statement to the patient is another major barrier (5). Simes (6) points out that

whatever recommendation is made by the physician, the final decision of trial participation rests with the patient. However, in order to make an informed judgment, the patient first needs to know something about the risks and benefits of each treatment option. While it appears that most cancer patients want to be involved in decisions about their care, there is still considerable debate on just how much information the patient should be given. However, the stressing of how *much* information is communicated rather than *how* that information is communicated may be counterproductive for the patient trying to understand complex risk-benefit relationships.

Medical ethics demand that a patient know and understand enough about a study and its potential risks and benefits to be able to make a free, informed choice about participating in it. Informed consent involves an ongoing process of communication between patient and health professionals. Usually, this requires explaining complex, unfamiliar technical information to a frightened patient who is under the stress of a life-threatening illness.

*See "Notes" section following "References."

A number of reports have shown that truly informed consent is difficult to achieve. Informed consent and patient recall of information about clinical trials can be problematic (7-9). Some patients have not understood the purpose or nature of their treatment, although they signed informed consent forms (7-10). Some others, who also signed the forms, afterward did not know they were participating in investigational treatment (11,12).

BOOKLET DEVELOPMENT

Early in the 1980s, NCI investigated the educational needs of cancer patients considering clinical trials and how to meet these needs. An initial survey indicated that few educational materials explained clinical studies to patients, and no publication was found that broadly addressed the major issues of clinical trials in lay language.

A needs assessment for such materials was conducted with a sample of 53 subjects (13). The sample included cancer patients currently in trials, family members, physicians, oncology nurses, NCI cancer-control staff, social workers, and a health educator. The following were the main issues noted in common by the subgroups in the sample (both lay members and health professionals):

- Patients considering entering a clinical trial were usually under great stress and had difficulty grasping and remembering information. There was a need for educational materials to help them understand and retain complex information during this time.
- Patients considering entering a trial indicated little or no understanding of what trials were.
- Patients should be encouraged to ask questions about trials, but they often did not know what to ask.
- Patients were afraid they would be used as "guinea pigs" for research in an impersonal health-care system. (Once they were in a trial, the patient sample said, they found that this was not the case.)
- Clinical trials were important for medical progress.
- Respondents said that patients viewed participating in trials as being potentially helpful to themselves and to others who might benefit in the future.
- Patients and health-professional respondents said that it would be useful to develop a booklet with basic information about clinical trials. This could be used to reinforce patients' communication with health professionals and could be taken home for reference and sharing with family members.

Following the needs assessment, NCI developed the booklet "What Are Clinical Trials All About?" to address what patients needed and wanted to know as identified in the assessment. To aid readability and recall, the booklet was written in question-and-answer format, and the information was presented simply and in short segments. A glossary with phonetic spellings and a set of questions that patients should ask were included.

NCI was interested in increasing accrual to clinical trials, and the booklet was viewed by some as an educational tool that might also help increase accrual. It was clear at

the outset, however, that the booklet's main goal was to increase patients' knowledge and understanding of NCI-approved clinical trials, a topic that was complex and foreign to many.

The important consideration was to write the booklet so that informed decisions might be made by patients without undue influence or promotion. Achieving this turned out to be extremely difficult, involving many discussions and a new understanding of the delicate nuances of "influence" that could subtly threaten self-determination. For example, in some cases what seemed to be a straightforward description of a clinical trial from a researcher's point of view—illustrated by the words of patients describing their experiences in trials—overrode the objectivity demanded by the informed consent process.

Such problems were pointed out by the National Institutes of Health (NIH) Office for Protection From Research Risk and the Food and Drug Administration. Their comments helped to reshape and direct the booklet, so its neutral explanation of trials would protect and enhance, not override, the informed consent process. Because the booklet broke new ground, it was carefully reviewed by those groups and by NCI staff, the head of an Institutional Review Board, and individuals from the NIH legal counsel's office and the American Cancer Society.

The booklet went through a number of revisions, and important lessons were learned. It was then pretested with individuals outside of NCI who represented the target audiences. The booklet and a self-administered questionnaire were sent to a sample of 90 people: patients enrolled for at least 3 months in clinical trials, cancer center-based physicians and nurses, and NCI Cancer Information Service (CIS) staff. At that time, the issue of asking patients to answer a questionnaire about clinical trials was sensitive enough that a major cancer center refused to assist with the pretest.

In the pretest, the overall response to the booklet was positive. A substantial majority of respondents said the booklet accomplished its main purpose—to help cancer patients understand what clinical trials are. They indicated that the booklet

- Offered a comprehensive, understandable explanation of clinical trials.
- Answered the major questions patients would ask about clinical trials.
- Adequately described and clarified both the risks and the benefits associated with trials.
- Was factually correct.

Other comments called for revisions to further simplify the material, shorten the write-ups, and lower the reading level to grade nine, and these changes were made.

In 1985, the booklet was published as a new tool to help patients make informed decisions about participating in clinical trials and to assist health professionals in presenting objective information about these trials. The hope was that sensitivity by health professionals to the information needs of cancer patients, supplemented with good educational tools, would encourage informed decision making by patients. Since publication, the booklet has provided a

balanced framework for health professionals explaining a complex topic to highly stressed cancer patients trying to make difficult treatment decisions. It may have clarified for health professionals some of the ethical rights of patients as well.

RESEARCH METHODOLOGY

The present study evaluated the booklet's impact on cancer patients eligible for participation in clinical trials. North Memorial Medical Center, Minneapolis, Minn.; the CIS regional offices at Sylvester Comprehensive Cancer Center in Miami, Fla., and Fox Chase Cancer Center, Philadelphia, Pa.; and the NIH Clinical Center cooperated in the study. In all, 397 patients were randomly assigned either to the experimental group, which was immediately given the booklet, or to the control group, which was not given the booklet until after a posttest.

The North Memorial Medical Center and the Sylvester Comprehensive Cancer Center chose to define as eligible any cancer patient who *theoretically* would be eligible for clinical trials in general (open eligibility). Cancer patients with a stage and type of disease for which one or more trials were recruiting were considered eligible. In practice, this included any cancer patient who had measurable disease and had not received definitive treatment. Fox Chase Cancer Center and the NIH Clinical Center included cancer patients who were eligible for a *specific* clinical trial and who were actively considering participation in a specific trial (strict eligibility). These patients already met the medical eligibility requirements for a specific trial.

To assess the booklet's impact, a brief informed consent statement was presented to each patient and oral agreement was obtained. Patients were randomly assigned by entering their names in a log that was precoded with randomly generated assignments to experimental or control groups. Experimental group patients ($n = 203$) were given the booklet and encouraged to read it. Control group members ($n = 194$) were not given the booklet until after the 2-week posttest.

Data-collection instruments included: 1) the log; 2) the informed consent statement form, which recorded the patient's age, sex, race, education, and degree of mobility; 3) a Confidential Medical Information form collected from the patient's chart, which included the name of the attending physician as well as cancer site, extent of disease, previous treatments, current treatments, and whether the patient was in a clinical trial after the posttest; and 4) a posttest interview administered by telephone 2 weeks after the initial contact. The posttest included items covering whether the patient had read the booklet and found it useful, as well as attitudes, knowledge, and behaviors toward clinical trials.

Statistical analyses comparing the control and experimental groups were completed using chi-square tests. In addition, stepwise logistic regression models were developed to determine how attitudes and knowledge were affected by assignment to the experimental group, eligibility

criteria, participation in a trial, education, age, sex, race, patient mobility, cancer site, and extent of disease. The models reveal the impact of each variable on the outcome while adjusting for the others. A separate model was developed for each of the attitude and knowledge items for which a statistically significant difference was indicated by the chi-square tests.

RESULTS

There were no significant differences between the control and experimental groups in age and sex distribution. Patients were highly educated: 43% had at least some college or technical-school training after high school. Most patients reported that they were capable of all normal activity, and none was completely bedridden. Breast, lung, colorectal, and genital system cancers were the most common.

The largest group of patients, 34%, had distant metastases at the time of the informed consent interview. Patients enrolled by the institutions using the strict eligibility criteria were significantly more likely to have distant metastases as compared with institutions using the open eligibility criteria ($P < .01$). No differences were found between the control and experimental groups in the proportion of patients who had distant metastases.

At the posttest, of the 199 people who said they saw the booklet (181 experimental and 18 control subjects), 157 (78%) said they read it (control subjects who read the booklet obtained it from another source). Of those who read the booklet, 49% read it cover to cover, and 32% said they read it more than once. Thirty-seven percent of those who read the booklet said they talked with someone about the booklet. The great majority of those who read the booklet found it informative, interesting, helpful, attractive, and easy to understand (Table 1).

Attitudes

Statistically significant differences (chi-square analysis) were found between the control and experimental groups in their responses to two of the three attitude assessment questions (Table 2): 1) Experimental group members were

Table 1. Reactions to the booklet "What Are Clinical Trials All About?"*

Assessment	Reaction, % of respondents	
	Very/somewhat	Undecided/not
Informative	94.1	5.9
Helpful	80.5	19.5
Understandable	94.8	5.2
Interesting	84.4	15.6
Attractive	79.9	20.1

*Responses were obtained from 157 people who said they read the booklet: 94% of the experimental group, 6% of the control group. (Control subjects who read the booklet obtained it from another source.)

Table 2. Responses of control and experimental groups to attitude assessment questions

Response	Control group, No. (%)	Experimental group, No. (%)
Is your understanding of clinical trials:*		
Very clear?	53 (27.3)	77 (37.9)
Somewhat clear?	52 (26.8)	72 (35.5)
Undecided?	33 (17.0)	19 (9.4)
Somewhat confused?	35 (18.0)	27 (13.3)
Very confused?	19 (9.8)	7 (3.4)
Refused	2 (1.0)	1 (0.5)
Total	194 (100.0)	203 (100.0)
Does knowing about clinical trials make you feel:†		
Very upset?	2 (1.0)	2 (1.0)
Somewhat upset?	7 (3.6)	12 (5.9)
Undecided?	83 (42.8)	62 (30.5)
Somewhat relieved?	60 (30.9)	82 (40.4)
Very relieved?	33 (17.0)	42 (20.7)
Refused	9 (4.6)	3 (1.5)
Total	194 (100.0)	203 (100.0)

*Chi-square, 17.75; $P = .001$ (computed without refusers). Percentages are rounded.

†Chi-square, 8.27; $P = .08$ (computed without refusers). Percentages are rounded.

more likely to feel somewhat or very clear in their understanding of clinical trials; control group members were more likely to be undecided and to feel somewhat or very confused. 2) Compared with control group members, the experimental group members were significantly more likely to feel somewhat or very relieved about knowing about clinical trials. 3) There was no difference between the groups on an item asking how hopeful or doubtful they felt knowing about clinical trials.

These chi-square analyses were also stratified by eligibility criteria. Patients eligible for a specific clinical trial (strict criteria) were significantly more likely to feel very clear in their understanding of clinical trials, to be very hopeful, and to be very relieved knowing about clinical trials compared with those theoretically eligible for trials in general (open criteria).

The logistic regression model showed that eligibility criteria, education, and patient mobility did affect whether patients felt clear or confused in their understanding of clinical trials. Being in the experimental group still had a major effect: experimental group members were about twice as likely to feel clear in their understanding as were control group members.

Knowledge

Ten statements were chosen to determine the patients' knowledge about clinical trials (Table 3). All the statements were based on information that was clearly stated in the clinical trials booklet. Six of the statements were true; four were false. Patients were asked to agree or disagree with each statement.

Experimental group members were significantly more knowledgeable in their responses to five of the 10 statements about clinical trials. These items revealed understanding of the voluntary nature of entering or leaving a clinical trial, that standard treatments may be as good as research treatments, that trials may cause side effects, and that clinical trials can be conducted in the same settings as those where standard treatment is given. For the item on the meaning of "randomization" (statement 9), there was also a significant difference between the two groups; surprisingly, experimental group members were more likely to answer incorrectly or to be undecided. We suspect that the wording of this item was confusing. Some patients may have understood the item to mean that their treatment would be chosen by chance from a great array of different treatments, rather than understanding that they would be placed by chance in one of the treatment groups within a specific trial. For the other four knowledge statements, there were no statistically significant differences between the experimental and control groups, although all these items show differences in the expected direction.

These items were also stratified by eligibility criteria. Patients eligible for a specific clinical trial (strict criteria) were significantly more knowledgeable for five of the 10 items compared with patients theoretically eligible for trials in general (open criteria). These items included understanding that remaining in a clinical trial is voluntary (statement 1, $P < .01$; statement 8, $P < .01$), understanding what "informed consent" (statement 2, $P < .01$) and "standard treatments" (statement 3, $P < .01$) mean, and knowing that patients in clinical trials do not have to go to a different place (statement 7, $P < .01$).

A simple combined score was developed, where each correct answer equaled 1 and each incorrect answer equaled 0, added over the 10 knowledge items. A t test of the score with group assignment indicated that being in the experimental group resulted in a significantly higher score than being in the control group ($t = -3.6$, $P < .01$). Patients entered under the strict eligibility requirement also scored significantly better than those entered under the open requirement ($t = 3.8$, $P < .01$).

Significant logistic regression models were developed for four of the knowledge items: 1 (staying in a trial), 7 (places to get care), 8 (stopping a trial), and 9 (randomization). The models demonstrated that eligibility criteria affected knowledge; patients entered under the strict eligibility criteria tended to be more knowledgeable. For knowledge items 1, 7, and 8, female patients were more likely to answer the items correctly than male patients, and younger patients did better than older patients. Education had surprisingly little effect. After adjusting for these variables, being in the experimental group still had a major effect. Experimental group members were from two to four times as likely to answer knowledge items correctly as were control group members. For item 9, on the meaning of "randomization," control group members were slightly more knowledgeable than experimental group members.

Table 3. Statements used to determine patients' knowledge about clinical trials

Knowledge statement*	No. (%) answering correctly		Chi-square
	Experimental group	Control group	
1) If I were to enter a trial I would have to stay in it until the trial is over.	139 (68.5)	77 (39.7)	34.49 ($P < .01$)†
2) "Informed consent" means that I am given information about the trial so I can freely decide whether to participate.	167 (82.3)	150 (77.3)	1.24 ($P = .54$)†
3) The treatments generally being used are called "standard treatments."	71 (35.0)	70 (36.1)	1.12 ($P = .57$)†
4) Standard treatments are never as good as new research treatments.	119 (58.6)	91 (46.9)	6.98 ($P = .03$)†
5) Treatments used in clinical trials may cause side effects.	187 (92.1)	167 (86.1)	5.63 ($P = .06$)†
6) It is up to me to decide whether to be in a clinical trial.	191 (94.1)	183 (94.3)	0.47 ($P = .79$)†
7) Patients in clinical trials must get their care at different places from patients getting standard treatments.	97 (47.8)	69 (35.6)	7.05 ($P = .03$)†
8) If I were to join a clinical trial, I could decide to stop at any time.	186 (91.6)	161 (83.0)	6.89 ($P = .03$)†
9) "Randomization" means that my treatment will be chosen by chance.	82 (40.4)	95 (49.0)	5.91 ($P = .05$)†
10) Once I join a clinical trial, my own doctor will not know what happens to me.	163 (84.0)	147 (72.4)	2.26 ($P = .32$)†

*Patients were asked to agree or to disagree with each statement. For statements 1, 4, 7, and 10, the correct answer was "disagree"; for statements 2, 3, 5, 6, 8, and 9, the correct answer was "agree."

†Computed without refusers, based on three response categories: agree, disagree, and undecided.

Patients with at least a high-school education were almost twice as likely to answer correctly as were those with less education.

Behaviors

The last section of the posttest covered the patients' behaviors toward clinical trials. As previously noted, patients were eligible for this study if they were eligible for a clinical trial but were not in a trial at that time. Patients were asked whether they were in a clinical trial at the time of the posttest (2 weeks after entry into this study), and patients' medical charts were examined to determine if the patient was in a trial or being considered for a clinical trial. There was no significant difference between the control and experimental groups in self-reported or chart-reported participation in clinical trials.

One interesting sidelight is that fewer patients reported being in a clinical trial than were shown to be in a trial based on chart review. One hundred sixty-three patients reported participating, and the chart review showed 210. This may be due in part to timing, because the chart reviews were often completed after the posttest, and patients may have been added to trials after the posttest. It also raises the question, however, of whether some patients were participating in trials without realizing it.

Not surprisingly, patients entered by institutions using the strict definition of eligibility (that patients must be eligible for and actively considering a specific clinical trial) were significantly more likely to be in a clinical trial at the posttest compared with patients entered by institutions using the open definition of eligibility (that patients be theoretically eligible for clinical trials in general). In other words, patients eligible for a specific trial were more likely to be participating in a trial. Analyses completed within each eligibility group found no differences in trial participation between the control and experimental groups.

Responses to the attitude and knowledge items were also analyzed by whether patients reported being in a clinical trial at the time of the posttest. Patients who reported being in a clinical trial were significantly more likely to feel clear in their understanding of clinical trials and were more hopeful. Patients in trials were also more knowledgeable on six of the items than were those not in trials. They understood the voluntary nature of trials (statement 1, $P < .01$; statement 8, $P < .01$), and they understood the meaning of "informed consent" (statement 2, $P < .01$) and "standard treatments" (statement 3, $P < .01$). They were aware that trials may cause side effects (statement 5, $P = .01$), and they felt their own doctor would know about their status after they joined the trial (statement 10, $P = .04$). This enhanced knowledge may

have been gained when these patients went through the clinical trials informed consent process. Unfortunately, we did not directly collect data on which patients had been through an informed consent process prior to the posttest.

Patients who reported not being in a clinical trial at the posttest were asked if they would ever consider participating in a trial; most remained undecided. There were no significant differences between control and experimental group members in their answers to this question.

DISCUSSION

The booklet "What Are Clinical Trials All About?" met its major objective—to increase patients' knowledge and understanding of clinical trials; this outcome implies that informed decisions could be made. In addition, the booklet appeared to supplement information provided in the clinical trials informed consent process; logistic regression models indicated, however, that for one of the knowledge items (see Table 3, statement 1), participation in a trial (and presumably going through an informed consent process before entering that trial) had less impact on answering correctly than did being assigned to the group which received the booklet. This points out the need for research on the adequacy of communication during the clinical trials informed consent process. We conclude that the booklet can be a valuable tool to aid health professionals in communicating about clinical trials with their patients.

Since its publication in 1985, over 1 million copies of the booklet have been distributed. It was the first step toward the major promotional effort later developed by NCI's Office of Cancer Communications to heighten the public's awareness of clinical trials as an important option in cancer treatment. The booklet also contributed core information and perspective for building the CIS training program on clinical trials.

In the United States and other countries, "What Are Clinical Trials All About?" has been a useful model for a number of organizations and institutions seeking communications tools to address issues relating to clinical trials for the general public and patients. These organizations include cancer centers in the United States, Canada, Europe, and Japan. The booklet has been translated into Japanese for planned publication in the *Japanese Journal of Clinical Pharmacology and Therapeutics*. In 1991, the booklet was published in Japanese in the journal *Clinical Evaluation* and as an appendix to the Japanese version of *Cancer Chemotherapy: An Introduction*, by T. J. Priestman (Berlin: Springer-Verlag). One editor commented to NCI that he hoped that the appendix would be helpful for "Japanese oncologists as well as patients." The interest of health professionals in the booklet is also indicated by its publication as an appendix to the chapter "Implementation of Clinical Trials" (by Jean Jenkins, R.N., M.S.N., and Dr. Greg Curt), in *Cancer Nursing: A Comprehensive Textbook* (Philadelphia: W. B. Saunders, 1990). The booklet has been used as a model for describ-

ing chemoprevention trials, and the Office of Cancer Communications is now planning to adapt it for special audiences, such as Hispanics and people with low literacy.

The booklet is currently available, and demand for it remains high. One lesson learned in developing it was how easy it can be to override informed consent in the enthusiasm of recruiting patients to trials. Promotion of clinical trials to heighten awareness of their importance and to help the public know about state-of-the-art treatment options is essential, but such promotion must be done carefully and thoughtfully. The right of each patient to make an informed choice about treatment must not be violated. Communicators who present clinical trial information to the public walk a thin line between informing and aiding self-determination on the one hand and prompting or unduly influencing on the other. Developing the booklet brought together experts from many areas to ensure that important facts were presented understandably with the objectivity called for by the ethics of patient care.

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Cancer Information Service Utilization by Selected U.S. Ethnic Groups

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The Cancer Information Service (CIS) has responded to information requests of more than 5 million people since 1976. Of interest to staff has been program coverage—in particular, patterns of use by audiences identified as being at high risk for cancer. This paper presents an introductory analysis of the use of the CIS between 1983 and 1990 by ethnic and racial groups. Data analysis, although affected by demographic data-collection restrictions, confirms suspected underutilization by racial and ethnic minorities. Although members of minority audiences call the CIS less frequently, they use the CIS for information about cancer-prevention topics more often than they do for treatment information, and their calls tend to be longer than calls from Whites. Television is demonstrated to be the most effective medium to stimulate use of the CIS among all audience groups. The authors conclude that expanding program coverage is important to reach target audiences, as is a more rigorous data-collection plan to assess utilization patterns. They also suggest the use of program funds to buy air time on a regular basis to stimulate use of the CIS by high-risk audiences and the general public. [Monogr Natl Cancer Inst 14:147-156, 1993]

INTRODUCTION

The National Cancer Institute's (NCI's) Cancer Information Service (CIS) has responded to the information needs of more than 5 million people since it began taking calls in 1976. Currently, the CIS receives over 500 000 calls yearly. This paper describes program utilization patterns by members of selected U.S. ethnic groups who called the service between 1983 and 1990. Sources of referral to the CIS, call length, education levels, and subjects of inquiry will be assessed among the ethnic groups to identify patterns and variances that may be useful to program planners in expanding program coverage.

BACKGROUND

The CIS was conceived in the mid-1970s by NCI to give cancer patients and members of the public immediate access to the latest information on cancer prevention, diagnosis, treatment, and rehabilitation.

From the beginning, Call Record Forms (CRFs) were developed and used by each local office. Data were collected by information specialists who documented the nature of each call as it was taken. Information on CIS calls

was compiled in five areas: 1) mode of inquiry (phone, mail, walk-in), 2) type of user, 3) type of question asked, 4) site or type of cancer involved, and 5) behavioral actions suggested to the caller by the CIS.

Initially, each office analyzed its local call data quarterly and forwarded summary reports to NCI for local and national trend analyses. Because national standards for data collection had not been mandated, there were no provisions to ensure uniformity of data or standardization of reporting. As a result, individual data programs were developed by the 17 local offices, all different in depth and quality. For several reasons, but primarily because of Office of Management and Budget (OMB) restrictions placed on collection of confidential data, no demographic questions could be asked in the early program years. Consequently, no demographic data were collected or available for program coverage analysis (1). During these years, individual CIS offices reported their impressions of low usage by the ethnic and minority populations in their service areas (many subsequently developed local programs and campaigns to reach these audiences), but this suspicion could not be validated without objective data on user demographics.

To address the need for uniform data collection and program analysis, a standardized CRF was adopted nationwide in 1983, and aggregate data began to be compiled. The new CRF—in addition to requesting information about such standard variables of each call as type of caller (patient, family member, person with symptoms, general public, "other"), nature of inquiry (e.g., diagnosis, treatment, prevention, resources), and behavioral suggestions made by staff—added demographic data questions. Specifically, callers were asked to designate their age range, education level, ethnic background, and source of referral.

Standardization of the database, in addition to producing individual profiles, enabled program planners to do cross tabulation analyses of type-of-inquiry variables with demographic variables to assess utilization patterns and caller profiles over time and among offices. Although CIS offices considered collection of demographic data important in assessing patterns of use among its users, including ethnic and minority populations, OMB restrictions limited the asking of demographic questions to a random sample of 20% of callers annually. This restriction, however, did not apply to CIS offices which were not funded by NCI or to offices which obtained other funding sources to support demographic data collection. The data described in the

*See "Notes" section following "References."

present study were captured in the database after the initiation of the standardized CRF. The authors acknowledge that demographic data collection has varied over the reporting period nationally and by local office, so the averages reported here may not represent experiences in various local offices.

At the same time that CIS offices began collecting demographic data to assess whether their perceptions of underutilization by ethnic and minority populations were correct, patterns of cancer incidence and mortality in these populations began to receive more attention. A report in 1983 to the President's Cancer Panel by Vincent T. DeVita, Jr., M.D., then Director of NCI, called the panel's attention to the disparity between cancer survival rates among Whites and those among Hispanic and African American populations and recommended increases in national resources for prevention and treatment programs to reach these audiences (2). An earlier study by the American Cancer Society (3) reported a lower level of awareness among African Americans about cancer risk factors and the ability of treatment to cure some cancers. A study by NCI's Office of Cancer Communications (4) described similar patterns among Hispanics. These findings reinforced the need for the CIS to look at its own utilization patterns in greater depth. In 1983 and 1984, demographic data, by then routinely collected following the OMB sampling plan, were assessed. Initial analyses confirmed what local offices had been reporting—underutilization of the CIS by various target audiences.

Concern about these early findings led NCI to initiate a broad-based cancer-prevention awareness program with specific messages and materials in English and Spanish about prevention, early detection, and risk factors targeted to Hispanics and African Americans, the two largest racial and ethnic minorities in America. Additionally, NCI authorized the formation of two new CIS task forces—an African American Audiences Task Force and an Hispanic Outreach Task Force—to work with NCI to develop relevant programs and materials to reach these audiences.

RESULTS

This paper reports general use of the CIS by various racial and ethnic groups (callers who described themselves as Native American, Hispanic, Asian or Pacific Islander, African American, or White not of Hispanic origin) between 1983 and 1990 and takes an in-depth look at specific promotional campaigns developed to increase cancer-prevention awareness among target audiences. Because the CIS sample size is so large, virtually any utilization differences discovered would be statistically significant. Thus, no formal tests of statistical significance are reported. The analysis of these data is made with acknowledgment of shortcomings of the data instrument, the sampling system, and potential data entry error.

Fig. 1 shows the total of CIS calls received between 1983 and 1990 ($N = 3\,200\,876$). Call volume jumped signifi-

cantly in 1984, when the 1-800-4-CANCER telephone number was adopted nationwide, and remained fairly stable over the next 5 years. A modest increase was seen in 1985, when NCI conducted several cancer-prevention campaigns with messages targeted specifically to African American and Hispanic audiences. Call volume jumped significantly in 1989, due primarily to promotion of the CIS number during Prostate Cancer Awareness Week and NCI's Mammography Awareness campaign.

Table 1 provides an overview of CIS call volume ($N = 1\,054\,783$) for the same 1983–1990 period for which demographic data (age, education, ethnic background) were collected. In all years, variances are observed between total call volume and the number of calls for which demographic data were collected. These variations can be attributed to changing guidelines of the OMB sampling plan for demographic data collection; variations in the numbers of offices collecting demographic data on all callers; the opening in late 1985 of the CIS Publications Ordering Service, which siphoned off publications requests formerly handled by the local offices; and fluctuations in total call volume.

Although the number of calls for which demographic data are available varied, apparently there was little variation in the percentage of use of the CIS by the various ethnic groups over the 8-year period. Use of the CIS by Whites accounted for roughly 88% of calls during this period. Use by African Americans ranged from 5.4% to 8.3%; the largest percentage of calls were received in 1985, the year NCI conducted a major cancer-prevention campaign targeting African American and Hispanic audiences. The number of calls from Hispanics was approximately half the number from African Americans and was relatively stable over the period at about 3%; the largest percentage occurred in 1989, when a major Spanish-language smoking-cessation campaign was initiated using a public service announcement (PSA) that benefited from significant air play during peak viewing periods.

During the 1983–1990 period, approximately 1.65% of CIS calls were from Asians or Pacific Islanders. Like the Asians or Pacific Islanders, the percentage of calls from Native Americans increased over the years, although their percentage of use is the lowest (0.49%) among these groups.

In a comparison of 1983–1990 CIS utilization patterns among ethnic groups, use by cancer patients was similar in all groups—between 15% and 20% of callers (Table 2). Within ethnic groups in the "patient" caller category, the greatest percentage of use was by Native Americans (19.5%) and the smallest was by Asians or Pacific Islanders (15.2%).

There was greater variation in use by friends and family members. Asian or Pacific Islander friends and family members were the most likely (25.2%) and African American callers were the least likely to call about illness in a friend or family member (14.5%). Friends and relatives of cancer patients used the CIS more than the patients themselves in all groups except the African American group.

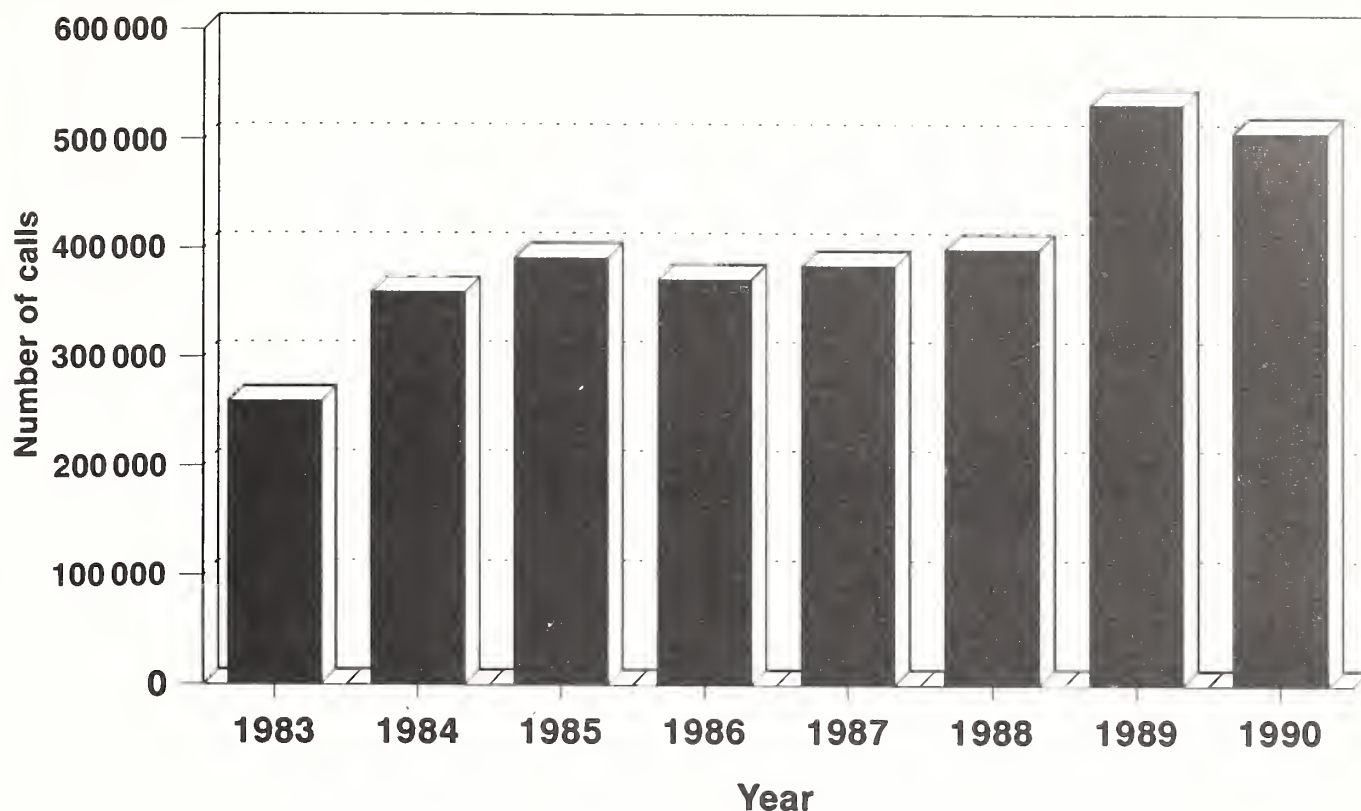


Fig. 1. Total CIS calls by year, 1983-1990.

Roughly 50% of all CIS calls during the 1983-1990 period were from members of the general public. General-public callers are categorized as those who are not symptomatic or sick but who have general questions about cancer, most often about prevention and early detection. The greater proportion of African Americans and Hispan-

ics in this category may be attributed to the fact that specially targeted CIS promotions during this period were about cancer prevention and smoking cessation, which are coded as general-public calls.

The "other" category of CIS callers includes health professionals and agencies, students, media representa-

Table 1. Total calls by year and race/ethnicity, 1983-1990
(N = 1 054 783)

Year	White		African American		Asian/Pacific Islander		Hispanic		Native American		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1983	67 872	87.96	5 698	7.38	1 013	1.31	2 281	2.96	299	0.39	77 163	100.00
1984	217 749	88.96	16 280	6.65	3 464	1.42	6 293	2.57	985	0.40	244 771	100.00
1985	222 154	86.74	21 181	8.27	4 119	1.61	7 709	3.01	957	0.37	256 120	100.00
1986	53 522	87.80	4 868	7.99	912	1.50	1 436	2.36	219	0.36	60 957	100.00
1987	100 604	88.94	6 657	5.89	1 870	1.65	3 571	3.16	414	0.37	113 116	100.00
1988	87 263	88.71	5 680	5.77	1 727	1.76	3 190	3.24	513	0.52	98 373	100.00
1989	99 519	88.24	6 099	5.41	2 049	1.82	4 348	3.86	771	0.68	112 786	100.00
1990	79 749	87.16	5 475	5.98	2 239	2.45	3 048	3.33	986	1.08	91 497	100.00
Total	928 432	88.02	71 938	6.82	17 393	1.65	31 876	3.02	5 144	0.49	1 054 783	100.00

Table 2. Type of caller by race/ethnicity, 1983–1990
(N = 1 054 783)

Type of caller	White		African American		Asian/Pacific Islander		Hispanic		Native American	
	No.	%	No.	%	No.	%	No.	%	No.	%
Cancer patient	174 107	18.75	12 877	17.90	2 648	15.22	5 185	16.27	1 003	19.50
Friend/relative	225 655	24.30	10 437	14.51	4 390	25.24	6 504	20.40	1 220	23.72
General public	455 309	49.04	38 667	53.75	8 573	49.29	16 773	52.62	2 421	47.06
Other	73 361	7.90	9 957	13.84	1 782	10.25	3 414	10.71	500	9.72
Total	928 432	100.00	71 938	100.00	17 393	100.00	31 876	100.00	5 144	100.00

tives and non-health-care professionals. Of the “other” callers, the largest proportion were African American and the smallest proportion were White.

In Table 3, potential inquiry topics are compared by ethnic group. For all callers, publication requests were the most common inquiry. This is not surprising, because a majority of CIS promotions during this period encouraged calling the CIS to order a pamphlet about a particular cancer-related topic. For Whites, the next greatest percentage of callers requested information related to a particular cancer site (18.3%). These differences may be linked to data in Table 2. Because a greater percentage of Whites were patients or family members, their interests would more likely be related to specific types of cancers.

For African Americans, Hispanics, and Native Americans, inquiries about smoking cessation ranked highest after publications requests—21.2%, 22.2%, and 23.9%, respectively. African Americans and Hispanics, who were more likely to be general-public callers, would be expected on that basis to request information on such topics as cancer prevention and smoking. Although Native Americans represented a lower percentage of general-public callers, they represented the largest percentage of calls concerning smoking cessation.

The increased percentages of calls about smoking by African Americans, Hispanics, and Native Americans may be attributed to smoking prevalence patterns and interest in quitting, as well as to the promotional campaigns conducted during the period. The U.S. Public

Health Service “Healthy People 2000” publication reports that smoking prevalence remains disproportionately high among African Americans—41% among males and 29% among females (5). The same report estimated Hispanic smoking prevalence at about 40% for males and 26% for females. For Native Americans, smoking prevalence rates were estimated at 42%–70%. These prevalence rates compare with the national average of 29%.

In 1985, NCI initiated its Cancer Prevention Awareness Campaign, which included several promotions targeted at African American and Hispanic audiences. One of the campaign’s major promotions targeted at African American audiences featured popular singer Aretha Franklin as spokesperson. Television and radio PSAs were produced, during which Ms. Franklin offered the message, “There is good news about cancer,” and encouraged people to learn the facts by calling the CIS to request the “Good News” publication. The PSAs were released, and stations were asked to air them for 6 months. The campaign was highly successful in stimulating calls, particularly from African Americans. Fig. 2 illustrates the calls related to this PSA. The campaign was initiated in June 1985, and the call level rose immediately. Frequency of calls attributed to the campaign reached a high of 583 per month 5 months after the campaign began and remained strong for 3 more months. Although some stations continued using the tapes after the 6-month requested airing period expired, when the PSA was no longer aired there was an immediate decline in calls from persons who cited the Aretha Franklin PSA as their source of referral.

Table 3. Subject of inquiry by race/ethnicity, 1983–1990
(N = 1 054 783)

Inquiry	White		African American		Asian/Pacific Islander		Hispanic		Native American	
	No.	%	No.	%	No.	%	No.	%	No.	%
Site information	170 943	18.41	9 868	13.72	3 195	18.37	5 397	16.93	941	18.29
Primary prevention	143 518	15.46	12 656	17.59	3 869	22.24	4 421	13.87	682	13.26
Smoking	165 032	17.78	15 220	21.16	2 482	14.27	7 065	22.16	1 232	23.95
Publications	277 444	29.88	23 698	32.94	5 593	32.16	8 304	26.05	1 346	26.17
Other	171 495	18.47	10 496	14.59	2 254	12.96	6 689	20.98	943	18.33
Total	928 432	100.00	71 938	100.00	17 393	100.00	31 876	100.00	5 144	100.00

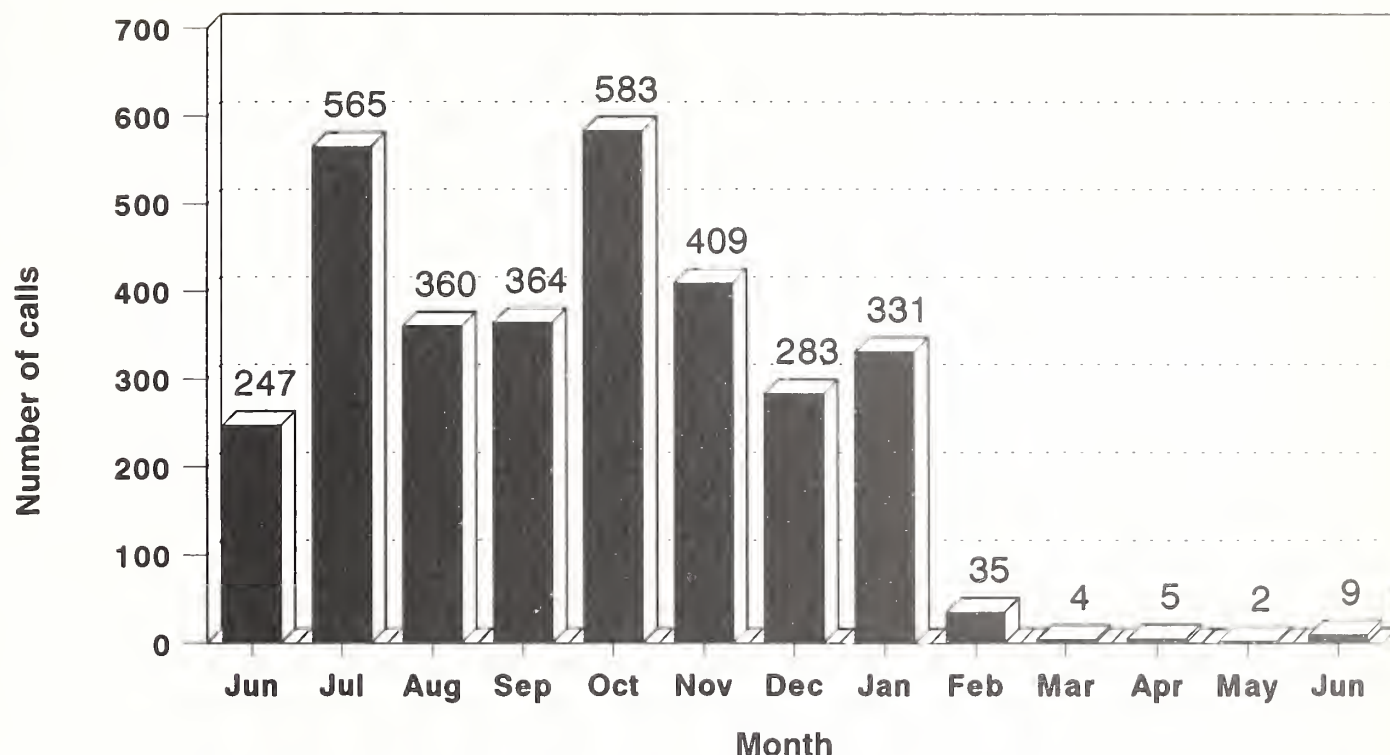


Fig. 2. Calls from African Americans as a result of the Aretha Franklin CIS campaign, 1985-1986.

Table 4 compares African American callers responding to the Aretha Franklin campaign and African American callers referred by some other source using the service in 1985. The data show that African American callers responding to the Aretha Franklin campaign reported slightly higher education levels than African Americans who called for other reasons. Although it was hoped that use of a spokesperson with broad appeal, such as Ms. Franklin, would stimulate prevention information calls to the CIS from African Americans with lower educational attainment, this did not occur.

Of ongoing interest to CIS program planners is how callers learn about the CIS phone number. Because of the limited financial resources available for program promo-

tion, traditional (mass media) and nontraditional (posters, grocery bags, bus and subway cards) media have been used to spread awareness of the 1-800-4-CANCER phone number. Fig. 3 (N = 948 456) analyzes how each caller first found out about the CIS, cross tabulated with ethnicity. Television was the predominant source for all ethnic groups except for Asians or Pacific Islanders. The discrepancy between television and other media is particularly apparent with African Americans, Hispanics, and Native Americans. This is not simply a reflection of the number of televised references, whether PSA, paid advertisement, or mention of the CIS on a television program, because there were almost the same number of television promotions as print promotions coded during this period (19 versus 18). This analysis demonstrates the power of

Table 4. Education level of African American callers during the Aretha Franklin campaign, 1985 (N = 17 743)

Education	African American callers responding to the Aretha Franklin campaign		All other African American callers		Total African American callers	
	No.	%	No.	%	No.	%
Some high school	411	14.99	2 462	16.41	2 873	16.19
High-school graduate	838	30.56	5 158	34.38	5 996	33.79
Some college	872	31.80	4 390	29.26	5 262	29.66
College graduate or more	621	22.65	2 991	19.94	3 612	20.36
Total	2 742	100.00	15 001	100.00	17 743	100.00

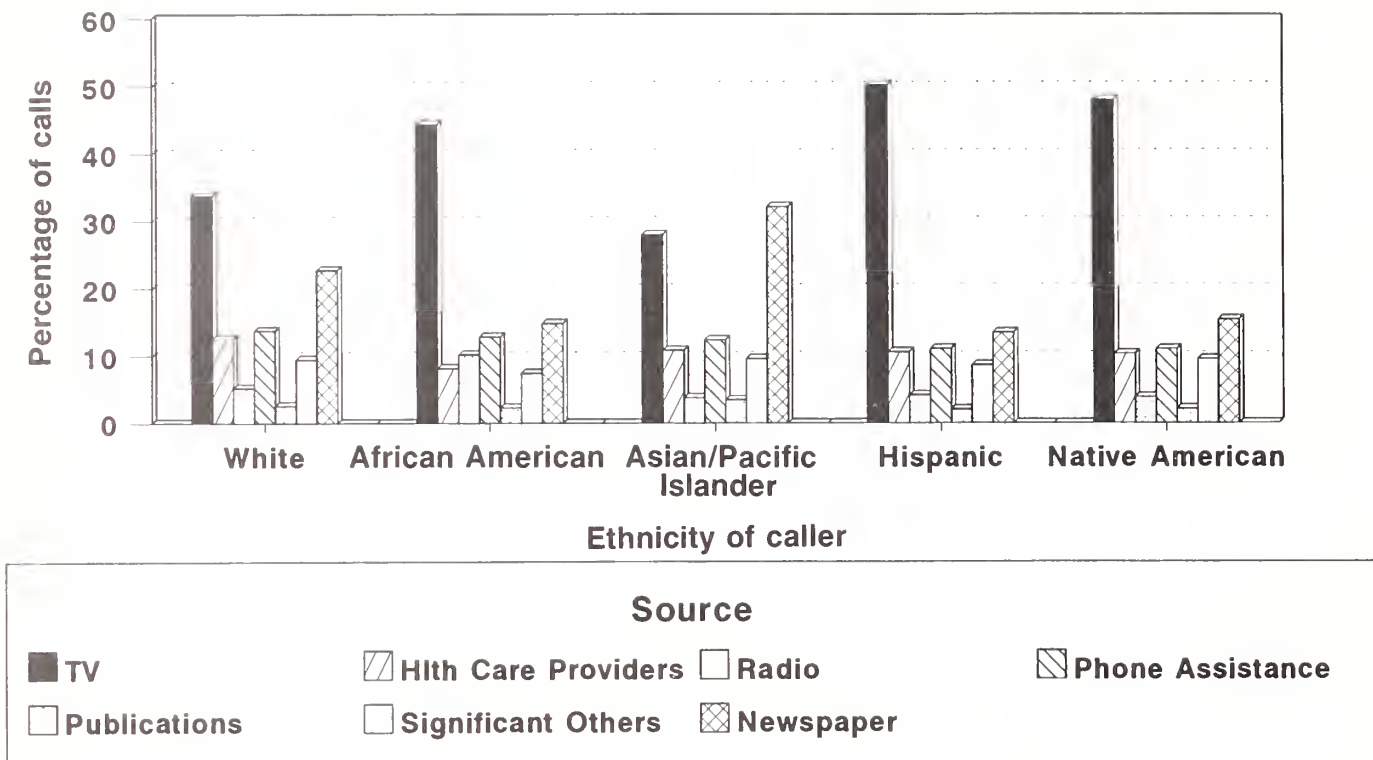


Fig. 3. How callers found out about the CIS (by ethnicity), 1983-1990.

television to stimulate action in the form of a health-seeking behavior—calling the CIS.

The next largest source of referral to the CIS was the newspaper. The CIS offices routinely promote the CIS phone number for publication in newspapers. In addition, the number is frequently used as a source for readers to learn more about a newsworthy topic covered by the print media. The newspaper was discovered to be an important source for finding out about the CIS for all ethnicities, especially Asians or Pacific Islanders, who cited newspaper referrals more frequently than television. As is seen later in this article (see Fig. 6), Asians or Pacific Islanders also cited higher educational attainment than other groups. This finding is not surprising, because an increase in years of education is often correlated with greater use of print media for information.

For nearly all groups, phone assistance (telephone book or operators) and health-care providers were ranked nearly equal as sources of referral to the CIS. Radio was cited as a source more frequently by African Americans than any other group.

As discussed above, education played a role in how callers first became aware of the CIS. As seen in Fig. 4, a relationship also was noted between caller education levels and television as the source of referral to the CIS. As education increased, television as a source decreased. As education increased, other media were cited more frequently as referral sources, with newspapers being cited as the next most common referral source in all groups except

those with grade-school educations. Referrals from the phone book also generally increased as education increased.

The highest percentage of callers who were referred by significant others (friends, family members) were persons with a grade-school education. It is encouraging that persons with grade-school educations find the CIS approachable and helpful enough to suggest its use to others. This fact also suggests that word-of-mouth testimony is an effective method of stimulating calls to the CIS.

Ethnicity and call length were recorded for almost 1 million callers (Fig. 5, N = 938 588). A similar pattern of call length existed among all ethnic groups. More than half of the calls lasted 1-5 minutes, and nearly all lasted less than 15 minutes. The percentage of calls under 5 minutes ranged from 54% to 68%. African American callers had the highest percentage of short calls (68%), followed by Whites (62%), Asians/Pacific Islanders (61%), Hispanics (59%), and Native Americans (53%). Longer call patterns emerged among Native Americans; the percentage for all groups decreased at each subsequent category of call length, excluding Native Americans, for whom the number of calls in the >25-minute category equals those in the 16-25-minute category. CIS information specialists attempt to check caller understanding throughout the course of a call. Callers who have less initial knowledge and information about cancer or who have language differences will generally require more call time for explanations of the technical and medical termi-

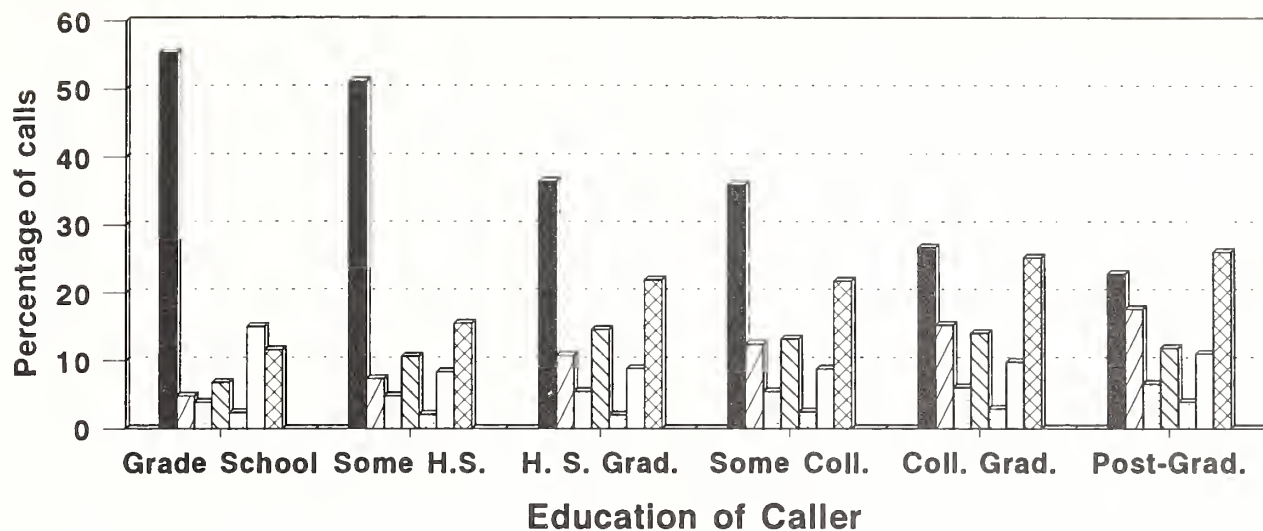


Fig. 4. How callers found out about the CIS (by education), 1983-1990.

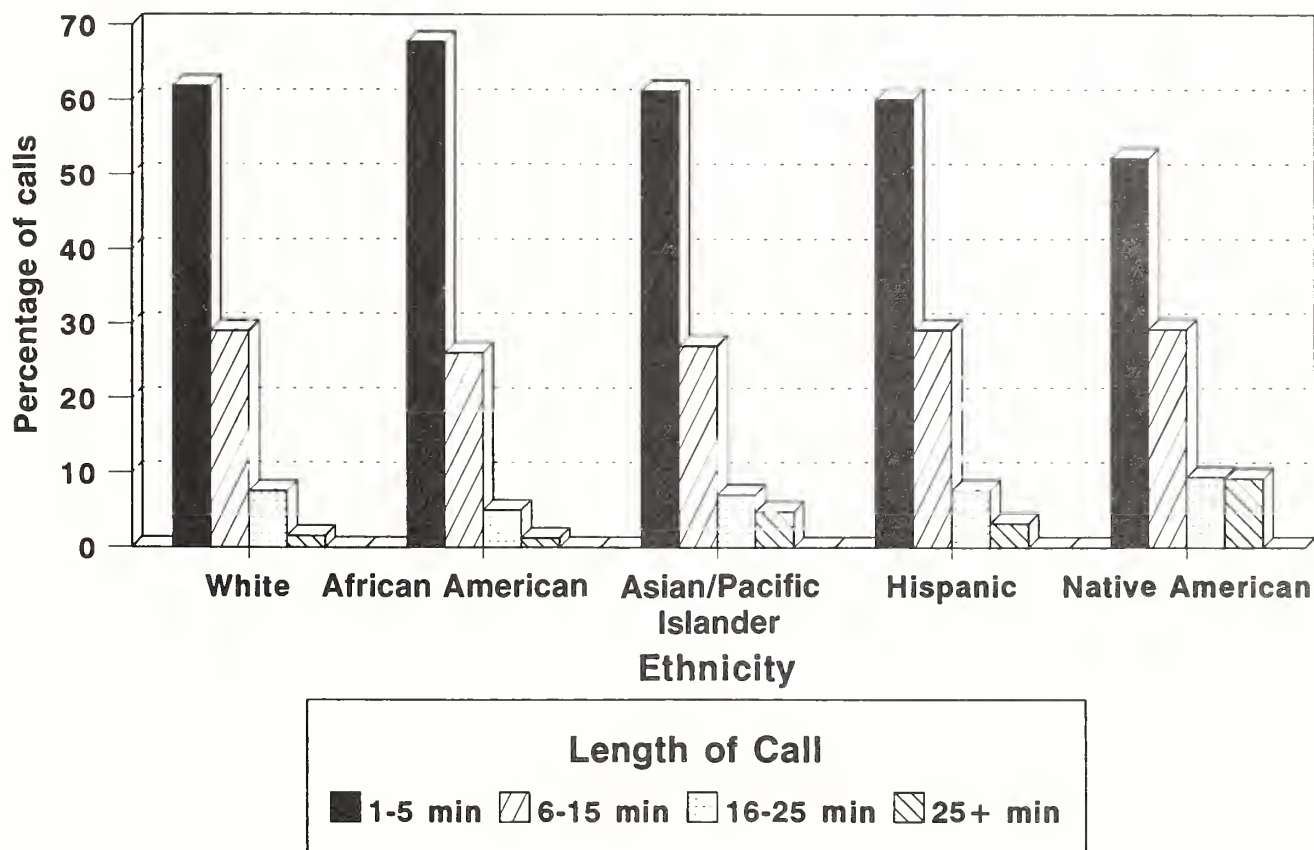


Fig. 5. Ethnicity and length of call for CIS callers, 1983-1990.

nology common to CIS calls and for verification of understanding.

As shown in Fig. 6, for Whites, African Americans, and Hispanics, the most common educational level of callers was high-school graduate, followed by "some college." The third most common educational level for African Americans and Whites was college graduate; for Hispanics, it was split between college graduates and "some high school." Asians or Pacific Islanders and Native Americans showed more variation. Asians or Pacific Islanders showed a higher overall education level; the most frequent category was "college graduate." The largest number of Native American callers reported "some college" background, followed by high-school and college graduation.

Cancer risk factors are frequently the focus of CIS communication campaigns. Because of the relationship of smoking to many cancer types, smoking-cessation campaigns have been conducted frequently throughout CIS history. In this study, we were interested in learning if there was a relationship between call length and ethnic background among callers seeking smoking-cessation information ($N = 434\ 247$). Table 5 ($N = 173\ 046$) describes variations in call length among ethnic groups. The majority of smoking-cessation calls lasted less than 5 minutes, with less than 1% lasting longer than 25 minutes. There appeared to be a tendency toward longer calls with Asian or Pacific Islander, Native American, and Hispanic callers than with Whites or African Americans; Native

Americans generally had the longest smoking-cessation calls.

The breast has been the cancer site most frequently called about throughout CIS history. Many of the breast-cancer-related calls between 1983 and 1990 pertained to prevention and early detection, including breast self-examination (BSE). Table 6 describes callers who used the CIS for information about BSE ($N = 6222$). More Whites called for BSE information than any other ethnic group. This is not surprising because the majority of people who use the CIS as a source of health information are White, and breast-cancer calls are the most common type of call received. African Americans were the second largest ethnic group to use the CIS for BSE inquiries, followed by Hispanics, Asians or Pacific Islanders, and Native Americans. Among all ethnic groups, the majority of calls were less than 5 minutes long; call length was shortest for Whites and longest for Native Americans. Roughly 42% of calls from African Americans were in the 6-15-minute range, accounting for the largest percentage of calls in that range. Although there were few calls from Asians or Pacific Islanders and Native Americans in this analysis, both groups tended to have longer calls.

Table 7 describes people who called the CIS to order publications about cancer ($N = 308\ 346$). Many called in response to promotions of the CIS offering free publications about cancer or its prevention. Bulk orders for publications (i.e., more than 5) are routed to NCI's Publica-

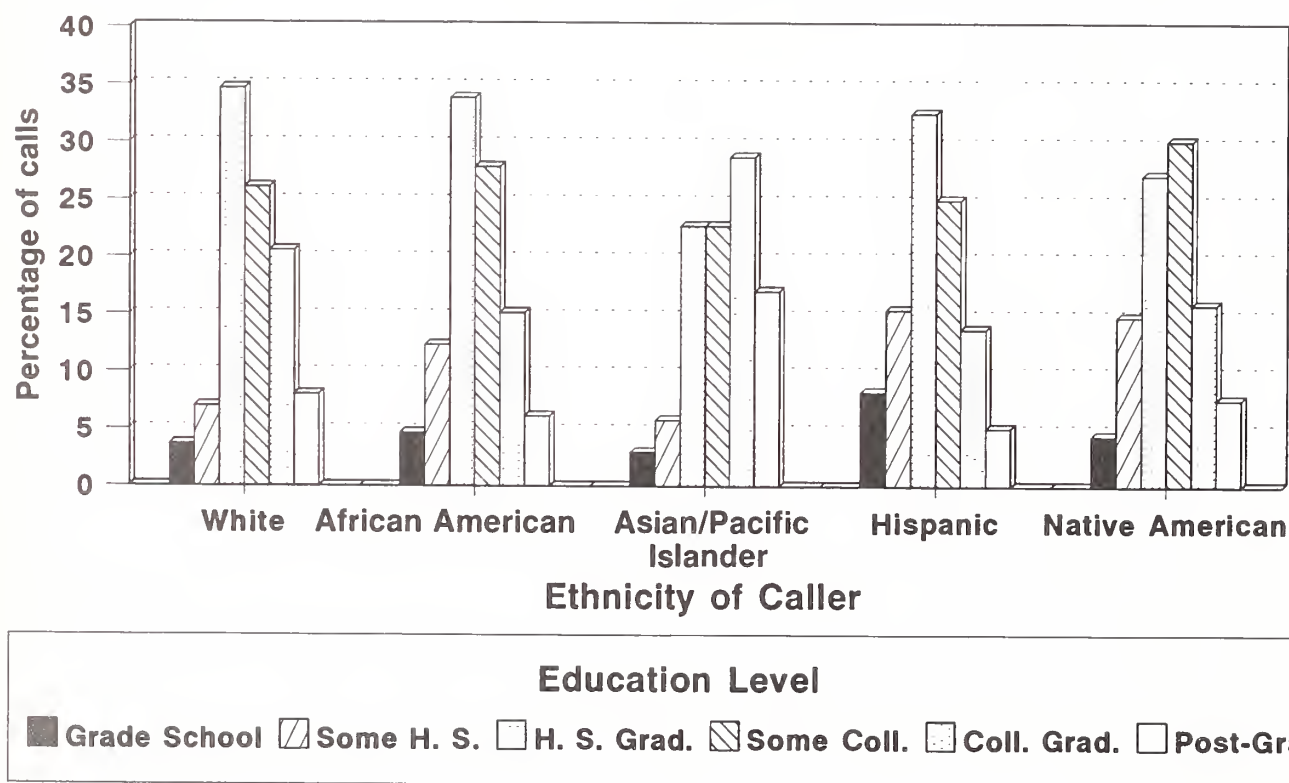


Fig. 6. Ethnicity and education level of CIS callers, 1983-1990.

Table 5. Percentage of calls concerning smoking cessation by call length (in minutes) by race/ethnicity, 1983-1990 (N = 173 046)

Race/ethnicity	1-5		6-15		16-25		>25		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
White	120 682	80.13	24 430	16.22	4 316	2.87	1 176	0.78	150 604	100.00
African American	10 321	80.66	1 963	15.34	365	2.85	147	1.15	12 796	100.00
Asian/Pacific Islander	1 787	77.23	355	15.34	50	2.16	122	5.27	2 314	100.00
Hispanic	4 496	72.46	1 285	20.71	303	4.88	121	1.95	6 205	100.00
Native American	786	69.74	207	18.37	60	5.32	74	6.57	1 127	100.00
Total	138 072	79.79	28 240	16.32	5 094	2.94	1 640	0.95	173 046	100.00

tions Ordering Service; orders for single publications usually are handled by the local offices. A pamphlet order call requires only the caller's name and address and the publication title, and so it would be expected that these calls would last less than 5 minutes. Yet, in every ethnic group, nearly 12% of the calls lasted longer than 5 minutes; some lasted more than 25 minutes. This indicates that although many people call the CIS to request a free publication, they actually have concerns about cancer which—when callers learn about the range of CIS services—can take significantly more time than a publication order alone. The length of calls from African Americans ordering publications were the shortest, 90% lasting 5 minutes or less, and calls from Native Americans were the longest, 21% lasting more than 5 minutes. Calls from Hispanics were the next longest; 14% lasted longer than 5 minutes.

CONCLUSIONS

It is evident from this introductory exploration of CIS patterns of use that the CIS is not reaching minority audiences as well as it is reaching White audiences. Although some promotional campaigns have been conducted to reach African American and Hispanic audiences in particular, campaign effects in terms of stimulating calls to the CIS are often short term. To increase the CIS's reach to these audiences, regular campaigns using appropriate media are recommended. Also apparent are the need for additional studies to assist program planners in using appropriate channels to reach target audiences and the need for research on ethnic groups' CIS usage in areas other than prevention.

In analyzing call length among ethnic groups for cancer-prevention and early-detection topics, we found evidence

Table 6. Percentage of calls concerning breast self-examination by call length (in minutes) by race/ethnicity, 1983-1990 (N = 6222)

Race/ethnicity	1-5		6-15		16-25		>25		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
White	3523	64.59	1510	27.69	285	5.23	136	2.49	5454	100.00
African American	205	53.39	163	42.45	14	3.65	2	0.52	384	100.00
Asian/Pacific Islander	37	51.39	28	38.89	4	5.56	3	4.17	72	100.00
Hispanic	175	58.33	106	35.33	14	4.67	5	1.67	300	100.00
Native American	6	50.00	4	33.33	1	8.33	1	8.33	12	100.00
Total	3946	63.42	1811	29.11	318	5.11	147	2.36	6222	100.00

Table 7. Percentage of calls requesting publications by call length (in minutes) by race/ethnicity, 1983-1990 (N = 308 346)

Race/ethnicity	1-5		6-15		16-25		>25		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
White	239 069	88.27	26 727	9.87	3 947	1.46	1 105	0.41	270 848	100.00
African American	20 266	89.54	1 997	8.82	262	1.16	108	0.48	22 633	100.00
Asian/Pacific Islander	4 820	87.86	501	9.13	65	1.18	100	1.82	5 486	100.00
Hispanic	6 956	85.97	876	10.83	131	1.62	128	1.58	8 091	100.00
Native American	1 013	78.65	166	12.89	34	2.64	75	5.82	1 288	100.00
Total	272 124	88.25	30 267	9.82	4 439	1.44	1 516	0.49	308 346	100.00

that health-information specialists spend more time on the phone with non-Whites than Whites. In general, it appears that BSE calls last significantly longer than smoking-cessation calls, even though both subjects are conducive to proactive behavior-change counseling (which would be expected to extend call length). This may be related to the fact that women calling about BSE may have additional questions related to breast-cancer symptoms and early detection, questions that can increase call length. Although a protocol to incorporate DiClemente and Prochaska's stages-of-change model in smoking-cessation calls was implemented in 1986, call length was not compared by year in this paper to determine if use of the model extended smoking-cessation calls (6).

There may also be a case for associating length of call with socioeconomic status rather than ethnicity. If education is used as a surrogate for socioeconomic status, one might conclude that a caller's education level might predict a need for more or less time on the phone, according to baseline cancer knowledge and need for explanation of more technical terms. In this study, longer calls more often came from minority callers than from Whites. Additional studies comparing call length, education, and ethnicity are recommended.

Data analysis strongly suggests that television is the most effective way of reaching the type of health consumers who are likely to use a telephone information service, across ethnic groups and education levels. Because so many of the CIS television promotions are free public service announcements aired at the discretion of television public service directors and frequently shown at times when the CIS is not open, program planners may want to lobby for revision of the policy that prohibits paying for television air time to promote the CIS. Paying for air time to reach viewing audiences at times when the CIS is open may prove to be an especially effective way of reaching target audiences.

If the promotions used over the length of the CIS program have not yet led to utilization across racial and ethnic groups, other methods may be needed to reach these underserved populations. It may be possible, for instance, to use the telephone service in different ways to reach lower socioeconomic groups, such as making outcalls ("cold calls") to targeted underserved neighborhoods. In addition, the new CIS Community Outreach Program (1) could prove to be an appropriate and valuable adjunct to the telephone service to ensure delivery of lifesaving cancer-prevention and early-detection messages to these audiences.

Another issue for program planners to address is the adequacy of the current evaluation plan to assess the program. Analysis of CIS use by various ethnic groups

and educational backgrounds currently is hampered by the lack of data on some callers. OMB may consider a 20% nationwide random data-collection plan adequate to provide an overall sampling of CIS use, but we concluded that it does not provide enough information to analyze the effectiveness of specific educational promotional campaigns. Targeted educational promotional campaigns are often short lived and may not occur near enough to the dates that random sampling occurs to capture campaign impact. Consistently measured patterns of use could enable program planners to assess utilization by the audiences for whom specific campaigns are developed. More conclusive analyses would be possible only if universal and continuous data-collection systems were implemented.

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Closing the Comprehension Gap: Low Literacy and the Cancer Information Service

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An estimated one in five Americans is functionally illiterate; they lack the literacy skills to access information or to perform many other basic tasks vital to their health and well-being. The National Cancer Institute and its Cancer Information Service have been working since 1990 to develop cancer-education strategies and materials to reach people with limited literacy skills. This paper reviews the link between cancer and illiteracy, the magnitude of the problem, and the association between cancer, certain health-related behaviors, and educational attainment. It also examines innovative National Cancer Institute and Cancer Information Service programs and materials designed to reach this high-risk population. [Monogr Natl Cancer Inst 14:157-163, 1993]

INTRODUCTION

A large number of Americans, particularly those of low socioeconomic status, lack the literacy skills to function adequately in our increasingly complex society (1,2). Functionally illiterate adults may experience difficulty applying reading, writing, computational, and information-processing skills to everyday life. Functional illiteracy cuts across race and class lines; however, "there is a significant correlation between literacy, education, and income levels" (3).

Studies show that Americans of low socioeconomic status have disproportionately high cancer incidence and mortality rates (4-6). Researchers theorize that these disproportionate rates are heavily influenced by lifestyle risk factors such as tobacco use, alcohol, a diet high in fat and low in fiber, occupational risks, and patterns of care related to early detection, diagnosis, and treatment (7). These lifestyle risk factors potentially may be influenced, however, by providing Americans of low socioeconomic status with culturally appropriate, understandable information that may promote cancer-prevention and cancer-control behaviors.

The National Cancer Institute (NCI) and its Cancer Information Service (CIS) have been working to develop effective cancer-education programs and materials for low-literacy audiences. In this paper, we review the magnitude of the literacy problem; the link between educational attainment and cancer risk; the need for low-literacy cancer-education materials, innovative CIS programs, and materials designed to reach low-literacy audiences; and future NCI-CIS activities.

MAGNITUDE OF THE PROBLEM

Until the results of the National Adult Literacy Survey (conducted by the Educational Testing Service in 1992) are available, the 1975 competency-based study by Northcutt et al. (1) provides the best available data on functional illiteracy among U.S. adults. Northcutt et al. estimated that one in five Americans (20%) is functionally illiterate. This estimate is based on measuring the competency levels of a random sample of 7500 adults in the knowledge areas of health, occupation, consumer economics, government and law, and community resources as well as reading, writing, problem-solving, and computational skills. Health-knowledge variables included 1) having a health-related working vocabulary that aids in reporting symptoms and following a doctor's directions, 2) understanding the constituents of a proper diet and planning nutritionally sound meals with available resources, and 3) planning for health or medical insurance and being aware of available financial assistance. The study found that 20% of the sample were functionally illiterate in the health-knowledge area, a finding that is consistent with the average for all knowledge and skills measured.

Data from the National Assessment of Educational Progress on the literacy skills of 3600 nationally representative 21- to 25-year-olds indicate that 80% function at or above the eighth-grade level (8). A number of studies have found a discrepancy of four to five grade levels between reported educational attainment and measured reading level (9-12). Thus, many of those who have completed the 12th grade could be expected to read at only an eighth-grade level.

In general, the problem of functional illiteracy is more widespread in minority groups and the elderly. Northcutt et al. (1) estimated that 44% of African Americans and 56% of Hispanics are functionally illiterate compared with 16% of Whites. A more recent national study found that "the literacy abilities of individuals aged 21 to 25 are unequally distributed by race and ethnic origin, and by socioeconomic status, with many minorities and low-income adults displaying disproportionately low abilities" (2). U.S. census data from 1989 show that there is a correlation between age and illiteracy. Among individuals 65 and over, African Americans are more than twice as

*See "Notes" section following "References."

likely to be functionally illiterate (defined as completing less than an eighth-grade education) than Whites (57.3% of African Americans compared with 27.4% of Whites) (13).

RISK BEHAVIOR AND ILLITERACY

It is estimated that approximately 80% of all cancer risk is attributable to specific lifestyle factors that individuals can change (14). There is substantive evidence that certain behaviors associated with cancer incidence and mortality are linked to an individual's level of educational attainment. A recent study (15) found that years of school completed, independent of other variables such as race and income, was a significant predictor for cancer-prevention/early-detection behaviors, including smoking status, dietary change, use of mammography, and stool blood test use.

Smoking Prevalence

The most solid predictor for the use of cigarettes appears to be education level. According to a 1985 study using National Health Interview Survey data (16), "... education has replaced gender as the major sociodemographic predictor of smoking status." Smoking prevalence decreased within all educational categories between 1974 and 1985, but the decline was much faster among educated people. Escobedo et al. (17) found that, compared with people who had graduated from high school, people with less than a high-school education were consistently more likely to have started smoking cigarettes during childhood and adolescence.

Breast-Cancer Screening

Data from a telephone survey in Massachusetts (18) showed that women with less than a high-school education were less likely than college graduates either to have had a mammogram at any time in their lives (38.6% versus 65.1%) or to have had a mammogram in the past year (21.5% versus 43.7%). In a similar survey, Rimer et al. (19) found that women ages 50-74 with at least a high-school education were more likely to have had two or more mammograms than women with less than a high-school education. These studies support National Health Interview Survey data that showed the proportion of women who had ever had a mammogram rose from 26% of those with less than 12 years of education to 48% of those with more than 12 years (20).

Cervical-Cancer Screening

Low educational status is associated with increased cervical-cancer incidence (21) and with decreased 5-year survival (6), two findings that may reflect better access to regular screening, follow-up, and treatment for those who are more highly educated. Two to three times as many low-income women (family incomes <\$15 000), who are

also likely to be less well-educated, report never having had a Pap test compared with higher income women (family income >\$25 000) (7). A public-health education program to improve screening for cervical cancer among urban African American women in North Carolina found that both age and education were predictors of behavior. Women with less than 12 years of education were 2.5 times less likely to have had a Pap test in the last year and were six to seven times less likely to know the purpose of this test compared with those who had 3 or more years of college. Level of education was the most important predictor of knowing that the Pap test screens for cancer (22).

Diet-Related Behaviors

NCI recommends a diet low in fat and high in fiber to decrease the risk of certain types of cancer. Few studies, however, have correlated food consumption patterns that might be important to cancer prevention with level of education. Results from the Minnesota Heart Survey indicated that, for women, higher education was associated significantly with intake of more carbohydrate and fiber and less fat and monounsaturated fatty acids (23). This study found similar associations between education and intake of both fiber and monounsaturated fatty acids among men. The correlations with education were independent of differences in income. Although this study does not specifically link food intake, educational attainment, and cancer incidence or mortality, it does provide data relevant to potential cancer risk.

Cancer-Education Literature

Most printed information about cancer prevention, early detection, and treatment is written at a 10th-grade reading level or above (12,24). The Virginia Literacy Council has estimated that approximately 50% of the U.S. adult population may not be able to read many NCI materials (25). An Ohio State University readability analysis of 85 NCI publications found that 68% required a 10th grade reading level or better (3).

A number of studies have highlighted the discrepancy between the reading and comprehension abilities of patients and the health-education materials they are given to read (9-11). Many clinics report that patient reading levels are between grades one and six (12,25).

To evaluate current educational materials on smoking cessation, Meade and Byrd (12) collected 49 pieces from major national health organizations and government agencies. The reading levels of these materials ranged from 3rd-grade to college level (median grade, 9.5); the median reading levels of patients who smoked, however, were 10th grade (measured by reported years of education) and 6th grade (measured by a word recognition test). The discrepancy between the reading levels of patient literature and the literacy skills of patients is notable. Like other health-related publications, smoking-education literature is meant to reinforce doctor-patient interactions and to augment oral instructions regarding smoking cessation

and, therefore, is useful only when the recipients can read and understand it.

Meade et al. (26) reported that patient comprehension of smoking-cessation literature could be improved by simplifying the literature. In their study, patients were divided into three groups: 1) those receiving a smoking-cessation booklet written at the 5th-grade level, 2) those receiving a smoking-cessation booklet written at the 10th-grade level, and 3) a control group receiving no booklet. Investigators developed pretest and posttest questions, based on the contents of the booklet, to evaluate patients' knowledge about smoking. All subjects were administered the questions. Results showed 13% better comprehension for the group that received the 5th-grade-level booklet compared with the group that received the 10th-grade-level booklet and an 18% better comprehension compared with the control group. These results support the need for continued development of educational materials at low reading levels.

NCI AND LITERACY

On a national level, little has been done to meet the cancer-information needs of individuals with limited literacy skills. Hearings held by the American Cancer Society (ACS) in 1989 indicated that cancer-education and outreach efforts are insensitive and irrelevant to many poor people (27). In addition, Freimuth et al. (28) found evidence that people of low socioeconomic status do not routinely call the CIS. To bridge these gaps, NCI has established the Low Literacy Cancer Education Program, charged with communicating cancer-prevention, early-detection, and treatment information to individuals with limited literacy skills. Efforts include convening the National Work Group on Cancer and Literacy, established to identify effective strategies for communicating cancer information to low-literacy audiences and to build networks between the cancer-control and literacy communities; developing innovative nonprint and print materials; providing technical assistance to government agencies and others working with low-literacy populations; supporting locally based breast- and cervical-cancer-education projects targeting women with low literacy skills; and exploring innovative methods, such as interactive computer programs, for reaching low-literacy audiences.

NCI's CIS outreach efforts targeting low-literacy audiences are an integral part of NCI's Low Literacy Cancer Education Program. Working closely with NCI staff, the CIS is taking a proactive approach to identifying and meeting the cancer-information needs of people with limited literacy.

THE CIS LOW-LITERACY OUTREACH GROUP

The mission of the CIS toll-free telephone service has always been to offer the general public, cancer patients and their families, and health professionals the most up-to-date cancer information available. In 1990, NCI ex-

panded the scope of the CIS by adding an outreach component with the specific aim of working through existing organizations (i.e., intermediaries) to provide cancer information to underserved audiences such as African Americans, Hispanics, the elderly, and people with limited literacy skills.

The Kentucky, Massachusetts, and West Virginia/Virginia CIS offices chose to focus their outreach efforts on low-literacy audiences for the following reasons:

- The regions they serve include large percentages of medically underserved, impoverished, and poorly educated individuals.
- Low literacy is a serious problem throughout these regions.
- Overall cancer mortality is high (ranked in the top 15 states) for all the states in these regions, with the exception of Vermont (7), which is served by the Massachusetts CIS office.

Outreach efforts include the following:

- Developing materials for individuals with limited literacy skills.
- Establishing regional and community linkages with public-health nurses, U.S. Department of Agriculture Cooperative Extension Service agents, and literacy program instructors.
- Collaborating with and creating teaching modules for Adult Basic Education (ABE) and literacy programs.
- Designing "train-the-trainers" programs to encourage interactive use of low-literacy materials.

The discussion below describes these endeavors.

LOW-LITERACY MATERIALS DEVELOPMENT

The West Virginia/Virginia CIS at the Mary Babb Randolph Cancer Center has addressed the lack of available low-literacy cancer-education materials by developing fact sheets that explain cancer-prevention, early-detection, and treatment topics. Each fact sheet gives the reader a clear behavioral message (e.g., eat less fat, protect yourself from the sun, get a mammogram) along with simple, practical guidelines for achieving the desired behavior. The fact sheets incorporate many recognized guidelines for developing low-literacy print materials.

The Centers for Disease Control's Breast and Cervical Cancer Mortality and Prevention program in West Virginia has adopted the fact sheets for use as part of its "You're Worth It" education campaign. This education effort, coordinated by the Mary Babb Randolph Cancer Center, uses the fact sheets as a tool for recruiting low-income, medically underserved women for breast- and cervical-cancer screening.

The low-literacy fact sheets, available from CIS offices throughout the country, were pretested extensively with the intended audience to ensure comprehension, attractiveness, and acceptability. The pretest questionnaire was developed using a model previously tested by NCI for use with low-literacy audiences. The West Virginia/Virginia CIS worked with NCI's Low-Literacy Program Coordina-

tor to develop a standardized process for administering the questionnaire.

The three CIS offices involved in the low-literacy initiative and the Tennessee, Michigan, New York, and Colorado CIS offices participated in pretesting the fact sheets with 423 individuals from a variety of ethnic and racial backgrounds in both urban and rural settings. Pretest sites included health departments, primary-care clinics, senior centers, hospital outpatient clinics, and a social services agency.

The pretests yielded valuable information which was incorporated into the final versions of the fact sheets. For example, respondents suggested using larger headings, making several changes in wording to clarify meanings, and adding the numerals for the CIS telephone number (1-800-422-6237 rather than 1-800-4-CANCER) to eliminate the task of translating letters to numerals. They also felt the number should appear at the end of each fact sheet (rather than just at the top) because people would be most motivated to call after they finished reading the material.

The final versions of the fact sheets developed by the West Virginia/Virginia CIS, for example, were written at the fourth- to eighth-grade reading levels (as analyzed by the Right WriterTM computer program). The fact sheets also embodied a number of important principles critical to making print materials comprehensible to people with limited literacy skills. These principles included the following:

- Employ active rather than passive voice. ("The sun causes skin cancer" rather than "Skin cancer is caused by the sun.")
- Write in a conversational style.
- Use short words and short sentences.
- Surround text with plenty of white space.
- Describe only what readers *need* to know to achieve the desired behavior.
- Use concepts readers can understand. ("The doctor will ask you about your health" rather than "The physician will take a medical history.")
- Illustrate important points with simple line drawings.

The Kentucky CIS, located at the Markey Cancer Center, has used a collaborative approach to develop low-literacy materials. In 1985, the Markey Cancer Center, the Kentucky Department of Health Services, and the U.S. Centers for Disease Control began a 5-year project to develop intervention strategies to increase the number of women getting Pap tests. The Kentucky CIS and the Kentucky Cancer Program Community Programs Division began examining cancer-education materials being distributed to the low-income, low-literacy population in eastern Kentucky. They found that print was the medium most widely used and that much of this information was written at higher reading levels than the intended audience could comprehend. Therefore, the Kentucky CIS developed a simply written Pap test brochure. The Kentucky Department of Health Services modified and printed this brochure, and NCI's Office of Cancer Communications used it as the basis for their brochure "The Pap Test: It Can Save Your Life!"

The CIS recognizes that even simply written print materials are not appropriate for nonreaders. Listening is a primary means of learning for many adults, but the spoken word is particularly important to those with low literacy skills. This makes audiotapes a potentially valuable tool for conveying health information. In Massachusetts, the CIS at the Dana-Farber Cancer Institute has collaborated with the Massachusetts Association for the Blind to produce audiotape cassettes and braille translations of the low-literacy fact sheets for distribution to the blind and visually impaired. According to one estimate, 30% of blind and visually impaired individuals may be functionally illiterate (West Virginia Library Commission, Services to the Blind and Physically Handicapped: unpublished data, 1991).

ABE/LITERACY PROGRAM ACTIVITIES

ABE services, English as a Second Language (ESL) programs, and literacy networks provide the CIS with access to low-literacy audiences. The Kentucky CIS and West Virginia/Virginia CIS have developed teaching modules on cancer-related topics specifically for use in these programs. The Massachusetts CIS will design such modules in the near future.

The Kentucky CIS began its work with literacy programs in early 1990 by forming the Cancer-Literacy Coalition in southeastern Kentucky. Members include representatives of local literacy councils, community-development organizations for women and children, district health departments, the Kentucky Literacy Commission, two District Cancer Councils, and the Markey Cancer Center Community-Based Research Program. Following the lead of the successful low-literacy parenting series published by New Readers Press titled "Let's Work It Out: Topics for Parents," the coalition developed interactive reading modules to be used in classroom literacy programs or in one-on-one instruction with low-literacy students in their homes. The modules contain basic information on breast and cervical cancer, screening guidelines, making appointments, and payment options, and they present stories, which emphasize decision-making skills, and activities to reinforce screening messages.

Once the modules have been evaluated and modified, they will become a required component of Kentucky literacy training programs. Recent legislation mandating the participation of all Aid for Families with Dependent Children recipients in either job training or literacy programs will increase the number of women entering formal literacy programs and will, in turn, increase the number of women who will have access to the cancer-related modules.

The modules developed by the West Virginia/Virginia CIS focus on cancer risk reduction, early detection, and treatment. They are the result of a collaborative effort between the West Virginia/Virginia CIS office at Massey Cancer Center and the Virginia Adult Basic Education Program. These comprehensive modules concentrate on

behaviors that can reduce cancer risk and on descriptions of cancer diagnosis and treatment. Each module includes a teacher's guide and instructional booklet. The CIS pre-tested these materials in ABE classrooms and in one-on-one literacy training programs in Richmond, Virginia. A pilot project to evaluate the six modules is now under way with approximately 1000 literacy students throughout Virginia. The pilot project will assess pre- and post-intervention knowledge and attitudes about cancer prevention, detection, and treatment; smoking behavior; and specific factual cancer knowledge. When the project is completed, the CIS will submit the modules to NCI for approval. The modules then will be disseminated through family literacy programs and work-site education programs as well as through the CIS network.

The Massachusetts CIS is collaborating with the Massachusetts Department of Public Health's Divisions of Chronic Disease Prevention and Refugee and Immigrant Health, and the World Education/System for Adult Basic Education Support, Inc., to bring cancer education to adults in literacy classes through the Massachusetts Cancer Education and Literacy Initiative.

The objective is to demonstrate the effectiveness of utilizing ABE and ESL programs to communicate breast and cervical-cancer early-detection information to people with low literacy skills. The literacy class teachers will serve as intermediaries to reach their students with cancer-detection information.

Existing breast- and cervical-cancer early-detection materials from NCI, ACS, and other community programs will form the basis for development of two learner-centered modules to be written at the third- to fifth-grade reading levels. The project will include a teacher's manual and training workshops for ABE and ESL teachers and counselors throughout Massachusetts. It will provide teachers with information on the specific topics and offer activity suggestions and evaluation criteria. Activities will ask students to take information to others in their communities, especially family members and friends.

Evaluation of the modules will assess students' comprehension of the information, their attitudes toward breast- and cervical-cancer screening, and their willingness to be screened. In addition, the project will examine whether the modules' effectiveness varies according to the type and make-up of the class (e.g., ABE or ESL, predominantly women or both sexes).

Because literacy classes are only one setting where the low-literacy population can be reached, the modules will be designed for use in other settings such as in senior centers and community health centers. Recommendations also will be developed regarding replicability of the project in other areas of the state and region.

TRAIN-THE-TRAINERS

The Massachusetts, Kentucky, and West Virginia/Virginia CIS offices implemented a train-the-trainers program to promote the intended audience's comprehension

of the low-literacy fact sheets. The CIS Outreach Coordinators selected intermediaries (e.g., public-health nurses, extension agents, literacy teachers) who reach women with limited literacy skills. The Outreach Coordinators developed a training presentation for the program administrators in intermediary agencies. At each training session, the Outreach Coordinators gave the administrators an outline of significant points to use for training staff in their agencies. The goal was to encourage staff to employ the fact sheets as part of their interaction with clients rather than simply to distribute them.

In another training approach that emphasizes one-on-one interactions, the Kentucky CIS has created the Mountain Surveillance and Counseling Outreach ("Mountain SC-Out") Program, a community-based, low-cost health intervention, to provide early-detection messages directly to rural, low-income women with limited literacy skills. The project trains local women as Mountain SC-Outs and provides them with a notebook containing cancer-education messages for the intended audience. The Mountain SC-Outs contact at-risk women in their communities through home visits, encourage them to participate in local health department screening programs, and facilitate their access to screening resources.

FUTURE NCI AND CIS EFFORTS

The new CIS contracts will provide regional CIS coverage throughout the country. These contracts will require all CIS offices to address the needs of low-literacy populations. Expanding the scope of CIS low-literacy outreach efforts will enhance NCI's ability to meet the cancer-education needs of individuals with limited literacy skills.

NCI's plan is that knowledge gained from CIS regionally based experiences with low-literacy populations, information gathered from the National Work Group on Cancer and Literacy, and lessons learned from developing and pretesting low-literacy cancer-education materials will be diffused by the CIS network to intermediaries working with low-literacy populations.

In addition, the CIS will contribute its expertise in low literacy to Appalachia Leadership Initiative on Cancer (ALIC) grantees. The CIS will serve as a resource for ALIC program leaders as they design and implement outreach interventions. The CIS's experience in developing low-literacy materials and intervention techniques will help the ALIC network to identify and address the communication barriers that prevent this population from following cancer-prevention and screening guidelines.

SUMMARY

A significant number of Americans have limited literacy skills. Low literacy is more prevalent among individuals of low socioeconomic status, a group that has been found to be at increased risk for cancer incidence and mortality. Most available printed cancer information is written at reading levels beyond the reading abilities of these individ-

uals. NCI's Low Literacy Cancer Education Program, the establishment of the National Work Group on Cancer and Literacy, and the CIS low-literacy outreach efforts demonstrate NCI's commitment to meeting the cancer-information needs of low-literacy audiences.

The CIS already has demonstrated its potential to reach low-literacy audiences. The Kentucky, Massachusetts, and West Virginia/Virginia CIS offices have developed cancer education materials written at the fourth- to eighth-grade reading levels and have implemented a training program for key intermediaries to encourage interactive use of fact sheets in clinics, homes, community centers, and other sites. The Kentucky and West Virginia/Virginia offices have designed teaching modules for use in literacy programs; the Massachusetts office will do so in the near future.

These efforts are designed to meet the cancer-information needs of low-literacy audiences by providing these individuals with materials that they can read and that are meaningful in their lives and by raising the awareness of and providing technical assistance to health professionals serving these populations.

The CIS will continue to aid NCI in its efforts to develop and disseminate cancer-education messages to low-literacy populations through the development of additional materials and the recruitment of new intermediaries.

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Older Callers to the Cancer Information Service

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Cancer incidence and mortality are disproportionately high in older adults, yet most public service campaigns have not been directed explicitly at this population. We analyzed Cancer Information Service (CIS) call data from the years 1983–1990 to characterize callers age 60 years and over. Of 1 091 809 calls from which the age of the caller was ascertained, 206 104 (19%) were from this age group. Most older callers learned of the CIS from the telephone book, television, and brochures or pamphlets. In addition, we examined calls specifically from 1990 to ascertain recent trends in CIS utilization. Comparisons also were made between callers 60 and older and those 40–59. Additional targeting could increase calls from older adults. [Monogr Natl Cancer Inst 14:165–169, 1993]

INTRODUCTION

The aging of the population is one of the dominant demographic trends in the United States. At the beginning of the 20th century, 4% of the population was 65 years or older. By the year 2030, one in every five Americans will be age 65 or older. The absolute number of older Americans will rise dramatically over the next several decades from 31 million older persons in 1990 to 65 million in the year 2030 (1). This trend toward more older adults has significant implications for cancer control because the incidence of most cancers increases with age. Overall, more than 55% of the new cases of cancer each year occur in older adults. Thus, more than half of the cancer cases in the United States are accounted for by the 13% of the population which is over age 65. The annual age-specific cancer incidence rate per 100 000 rises from 300 for persons age 45–49 to 1400 for persons age 65–69. It is not just the burden of incidence that is borne by older adults; 67% of cancer deaths occur in persons over 65 years of age (1).

In commenting on the state of cancer control and treatment for older adults, Yancik and Ries (1) noted that little has changed since the conclusions of a 1983 National Cancer Institute (NCI)–National Institute on Aging working group which stated:

There has been virtually no organized focus on what has been known for a long time—incidence of most forms of cancer increases with advancing age. Little evidence exists to document how older age affects control or treatment of cancer or how physicians attend to the differences that appear to be inherent in the management of elderly patients with cancer. . . . There are strong feelings, but no facts (2).

It is not surprising, then, that studies of older adults and their health providers show that both have knowledge and practice deficits regarding cancer prevention, early detection, and treatment (3–8). For example, many older adults are not aware of the benefits of quitting smoking at older ages (9), and older women are less likely than younger women to know the recommended screening interval for mammography or, in fact, to get mammograms (10). There still are no universally accepted screening guidelines for women age 75 and over.

The Cancer Information Service (CIS) operates a toll-free national telephone helpline for people of all ages. Recent evidence indicates that the CIS telephone service can play an important role in facilitating health awareness, even behavior change, when used in conjunction with media campaigns (11). Previous reports of CIS helpline utilization suggest, however, that callers to the CIS are primarily middle-aged (12). In light of this fact and the fact that older adults are more likely to have cancer and to die of it than are younger Americans, it is clear that older adults have underutilized the CIS.

Here, we analyze CIS call data to describe characteristics and usage patterns of older callers, as well as to make comparisons between older and younger groups of callers. Although “older” is defined generally as age 65 and older, the CIS classifies “older” as age 60 and over. Therefore, when “older callers” is used in this report the latter designation is indicated. Adults over age 60 represent a diverse group with great variation in functional status.

METHODOLOGY

Population

The caller population for our study consisted of those who made calls to the CIS from 1983 to 1990. Calls during which age was not obtained by the information specialist, for whatever reason, were excluded from analysis; this included persons who identified themselves as previous users of the service because demographics are not asked of these repeat callers. Callers were self-selected and, therefore, did not constitute a random sample of the population of older Americans. Thus, no inferences can be made about a larger population.

*See “Notes” section following “References.”

Measures

During each call to the CIS, an information specialist records information related to the call; data are gathered both actively, by direct query, and passively, depending on the item (e.g., caller's sex). Results were reported as frequencies based on data from the nationally standardized Call Record Form (CRF). Demographics were collected only on prespecified days, rather than for each call, in compliance with requirements of the Office of Management and Budget. Callers with missing data were not included in our calculations. The removal of these data was warranted because of the magnitude of demographic data not ascertained due to the sampling plan. Missing data are attributed primarily to the sampling plan, not to refusal of callers to provide information or to a lack of effort by the information specialists. Due to the random sampling plan for the collection of demographic data, information for older callers where age was ascertained is likely to be representative of all older callers to the CIS. Because of the large number of total calls, tests of statistical significance would have yielded significant results, but the results would not be informative. Thus, significance levels are not presented. To show the recent trends in CIS utilization, the CRF data from 1990 are also highlighted below.

RESULTS

Characteristics of Older Callers

Older callers were defined as age 60 and over, because the CRF classifies the oldest callers this way; in other words, it was not possible to obtain data sorted by refined age categories (e.g., 60–64, 65–75, and ≥ 76). Overall, in the subsample of 1091809 calls where age was ascertained, there were 206104 calls from people age 60 and over between 1983 and 1990, 19% of all calls received. The majority of older callers were White (95%), female (69%), and well educated (90% were high-school graduates; 47% had attended college). Forty-six percent of older callers were members of the general public, 25% were diagnosed patients, and 22% were spouses or relatives of patients, with 7% “other” callers.

The most frequent responses of older callers to the question, “How did you first find out about the CIS?” were the telephone book (11%), television (10%), and a brochure or pamphlet (9%). Although there were few gender differences in how these callers found out about the CIS over the 1983–1990 time period, there was a difference between how older males and females found out about the CIS in 1990. In 1990, women most often reported finding out about the CIS from television (13%), a brochure or pamphlet (12%), or a newsletter or magazine (11%); the top three responses for men were the multimedia Prostate Cancer Awareness Campaign (18%), a story on the “Good Morning America” network television program (17%)—several different stories giving the CIS telephone number (1-800-4-CANCER) appeared on

“Good Morning America” during the year—and a brochure or pamphlet (10%). The 1990 data provide important clues about who new users of the CIS may be in subsequent years. It also shows how responsive older callers may be to promotional campaigns.

In the 1990 data, there were racial differences as well: 16% of African American and 13% of Hispanic, Asian, and Native American callers reported learning of the CIS telephone number from television, compared with 11% of Whites. The percentage of African Americans who learned of the CIS from radio was five times that of other groups. Nine percent of Hispanic/Asian/Native American callers found out about the CIS from the newspaper, compared with 4% of African Americans and 5% of Whites. Callers with less than 12 years of education were twice as likely as high-school graduates to have learned of the CIS from directory assistance and more than four times as likely as college graduates.

The most common subjects of inquiry for older callers based on cumulative 1983–1990 calls were publication requests (16%), cancer-site information (11%), primary prevention (9%), treatment (6%), and diet/nutrition (6%). For the entire period, slight gender differences exist (Table 1). For males in 1990, however, the three most frequent subjects of inquiry, which were different from trends in previous years, were site information (17%); screening (16%); and the names of hospitals, clinics, and screening programs (10%). In 1990, females most frequently inquired about site information (15%); treatment (8%); mammography (7%); publications (7%); and names of hospitals, clinics, and screening programs (7%). CIS coding conventions may underestimate the number of female callers requesting screening information; for example, there are specific codes for pap smear (0.2%), breast self-examination (2%), and mammogram (7%) in addition to a general screening code (4%). It should also be noted that Medicare was not paying for screening mammograms during the period analyzed; this fact presumably lowered the number of requests for mammography information.

For 1990 calls, differences in education level were seen as well; the percentage of high-school graduates calling about screening programs was higher than that of callers with less than 12 years of education. Also, callers who had some college were more likely to call for information related to clinical trials (3%). The cancer sites most often mentioned by older callers requesting site-specific information were prostate (33%), breast (26%), and lung and trachea (6%). Not surprisingly, this differed by gender. Male callers most frequently requested site information related to prostate (60%), breast (7%), colon (5%), and lung and trachea (5%); females most often called concerning breast (39%), prostate (14%), and lung and trachea (7%).

The most common behavioral suggestions or referrals to older patients in 1990 were to read literature (31%), talk to or visit your physician (12%), and contact a hospital or clinic (11%). The percentage of men referred to a screening program was four times that of women. This difference may, in part, be attributed to the success of certain

Table 1. Most frequent subject of inquiry, callers age 60 and over, by gender, 1983–1990*

Subject of inquiry	Rank	
	Females	Males
Publications request	1	1
Site information	2	2
Primary prevention	3	3
Diet/nutrition	4	5
Treatment	5	4
Physician referral	6	6
Smoking	7	7
Screening	8	10
Chemotherapy	9	11
Hospitals	10	9
Clinical trials	11	8

*Based on total number of subjects of inquiry of older callers by gender, females (n = 257 839) and males (n = 116 954). The CRF allows multiple responses per caller.

male-targeted screening campaigns in 1990, such as Prostate Cancer Awareness Week, rather than any bias in referrals, but this cannot be determined from the data. The percentage of women callers told to “share cancer information with other person” was twice that of men (8% versus 4%). Also, the percentage of female callers in 1990 who were spouses or relatives of cancer patients was more than twice that of male callers (27% females versus 13% males). Women often have been described as keepers of family health. As such, it is not surprising that they would call to obtain information related to a family member’s illness.

Comparisons With Younger Callers

We examined the bivariate relationships of older callers to callers 40–59 years of age. Demographic factors were slightly different across age groups for 1983–1990 calls (Table 2). The most notable difference between the older and the younger groups was the type of caller (Table 3). As expected, the percentage of callers who were diagnosed patients increased with age (25% of older callers versus 17% of those 40–59).

In 1990, differences between older and younger callers included the subject of inquiry and site-specific inquiries. Smoking-related calls constituted 4% of the inquiries made by callers age 40–59 and 2% of the inquiries made by older callers. Smoking-cessation campaigns sponsored by the Centers for Disease Control’s Office of Smoking and Health specifically targeted to older audiences did not begin until the end of 1990. For calls during which site-specific information was requested, there was an association between age and site specified. Younger callers most frequently called about breast cancer (32%), followed by cancer of the prostate (18%) and lung/trachea (8%). As mentioned previously, the 1990 call data indicated that older callers most frequently requested site information related to the prostate (33%).

Table 2. Demographic characteristics of callers 40–59 years of age and age 60 and over, 1983–1990*

Characteristic	Age group, %	
	40–59 y	≥ 60 y
Sex		
Male	25	31
Female	75	69
Ethnic background		
White, not of Hispanic origin	90	95
African American	6	3
Other	4	2
Education		
< 12 y	6	10
High-school graduate	37	43
Some college	27	22
College graduate	30	25

*Based on total number of 1983–1990 calls where age was ascertained, 40–59 y (n = 339 660) and ≥ 60 y (n = 178 842), with missing responses removed from calculations.

DISCUSSION

The data presented here show that trends prevalent in calls to the CIS more generally are exaggerated among older adults. Thus, as a group, callers age 60 and over are disproportionately White, female, and well educated. Older callers are underrepresented in relation to the proportion of cancers they experience. Nineteen percent of callers are older, although more than half of cancers occur in this age group. The 1990 data are unusual because there is a larger percentage of older callers (24%) than in previous years. This probably reflects the increased targeting of older adults through NCI’s Office of Cancer Communications. These results show that older adults respond positively to special promotional campaigns. Innovative outreach activities will be needed to motivate calls from specific older subgroups, including minorities, those with less formal education, and men. The Prostate Cancer Awareness Campaign is an example of a strategy that appeared to break through men’s usual reluctance to use the CIS. This campaign appeared to be especially effective in motivating calls from men, and more needs to be learned about why they responded. Consistent with other

Table 3. Type of caller by age group, 1983–1990

Type of caller	Age group, %	
	40–59 y (n = 362 410)	≥ 60 y (n = 202 272)
General public	46	46
Diagnosed patient	17	25
Spouse/relative of patient	27	22
Symptomatic person	6	5
Spouse/relative of symptomatic person	2	1
Other	2	1

studies of the mass media, our study determined that television was an important source of information for those who called the CIS, especially for minorities and women. The importance of radio as a source of information for minorities, however, suggests this may be a cost-effective resource for promotion, inasmuch as the cost of paid television time is often prohibitive.

RECENT PROGRAMS

In response to the growing problem of cancer in older Americans, NCI initiated a cancer-education program in the spring of 1991 targeted to those 65 and over. It became a part of NCI's multifaceted approach to addressing cancer among this population.

The goal of the education program is to help reduce cancer mortality in older Americans by providing information related to cancer prevention, early detection, state-of-the-art treatment, and follow-up care. Messages are disseminated through two major channels: mass media and intermediary organizations. The CIS plays an integral role in both of these areas.

In April 1991, the CIS established a Working Group on Older Americans, comprised of 10 CIS offices that targeted their older audiences for special outreach efforts on breast-cancer detection. Working closely with NCI's Office of Cancer Communications, the working group helped develop print public service announcements, news articles, letters to the editor, an early-detection brochure, and a guide for conducting talk shows.

In October 1991, NCI, the CIS, and the American Association of Retired Persons (AARP) collaborated in sponsoring a campaign to educate older women about mammography benefits under Medicare. They were joined in this effort by the National Institute on Aging, the Centers for Disease Control, and the Health Care Financing Administration.

The joint campaign generated a national press conference, a video news release, television and radio public service announcements with celebrities such as Angela Lansbury and Ruby Dee, a mammography brochure for older women, a fact sheet on Medicare coverage, and articles in AARP publications, which reach over 30 million members.

The CIS offices provided their local stations with the public service announcements, and CIS outreach coordinators were urged to link up with AARP Health Advocacy Volunteers to conduct local programs throughout the country.

By mid-1992, the structure was in place for ongoing, long-term education outreach efforts from NCI and the CIS offices targeting older Americans. In future years, the CIS activity should be expanded to address other cancer issues, such as prostate cancer and cancer education for older patients. An evaluation component of the program will assess whether there is an increase in the number of calls from older Americans.

CONCLUSION

The CIS is an excellent source for answers to cancer-related questions. If, however, the CIS is to gather useful information for tracking the impact of campaigns on older callers, as well as for targeting different subgroups of the 60-and-over population, it is crucial that more refined age categories be used to characterize older adults. Callers in the older-old age groups might be expected to have somewhat different concerns from those in the younger-old age groups (13).

Moreover, for the CIS to serve the needs of older callers, especially minorities (5% of older callers, 1983-1990) and those with less than a high-school education (10% of older callers, 1983-1990), special outreach, such as that which occurred during the Prostate Cancer Awareness Campaign, may be needed. Radio and television have been effective, promising avenues for promotion. As suggested by Anderson et al. (14), television also may help to close the gap between callers who are highly educated and those who are less educated. The ideal use of the CIS is as an adjunct to multistrategy campaigns that involve the mass media, health professionals, and interpersonal channels such as peer leaders in the community. Finally, some recent experiences (15,16) suggest that in the future the use of proactive counseling using CIS counselors may have an important role to play in reaching populations that do not ordinarily call the CIS. Rimer et al. (17) showed that proactive telephone calls to older smokers increased 3-month quit rates. Such strategies can be extended to reach underserved populations in the United States who consistently remain underusers of the CIS.

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Information-Management Technology in the Cancer Information Service

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This paper identifies the potential applications of information-management technology in the Cancer Information Service national network and describes some innovations of individual network offices in each area. New applications are explored and recommendations are made for coordinating these efforts nationally. [Monogr Natl Cancer Inst 14:171-176, 1993]

INTRODUCTION

The Cancer Information Service (CIS) telephone service is the National Cancer Institute's (NCI's) primary mechanism for disseminating information on the prevention, diagnosis, and treatment of cancer. In addition, through its community outreach program, the national network of CIS offices is charged with the assessment of regional cancer-education needs (based on local data) and identification of high-risk populations appropriate for targeted education initiatives. Both program components require the development of regional resource directories including information on cancer-related community programs and services, intermediary organizations, and media outlets. To meet these program objectives, CIS staff must access, process, interpret, organize, update, and evaluate a wide range of information resources.

The virtual explosion of technology in telecommunications and computerized information management has widespread application to the CIS program. Several local offices have individually taken advantage of this technology in a variety of applications. The CIS, however, has lacked a national strategic plan—and the resources—for coordinating a network-wide introduction of this technology. This has fostered the preservation of paper-based systems in many offices and a piecemeal approach to the application of information-management technology. Although the individual innovations of network offices have been significant, the lack of a national plan for coordinating these efforts has resulted in the development of sometimes duplicative and incompatible systems. Because of this experience and because of the availability of emerging technologies, however, the CIS program is well positioned to develop a more strategic approach to the development of uniform and integrated information-management systems to enhance efficiency and productivity.

Several CIS program functions can benefit from information-management technology: 1) providing callers with rapid access to a trained information specialist, 2) disseminating accurate, up-to-date information, 3) developing and using community resources, 4) managing the

program, 5) conducting community outreach, 6) providing training, 7) ensuring quality control, and 8) evaluating the program. This paper identifies the potential applications of information-management technology within the CIS and describes some innovations of individual network offices in each area. New applications are explored and recommendations for coordinating these efforts nationally are provided.

PROVIDING RAPID ACCESS TO TRAINED INFORMATION SPECIALISTS

The quality of the service provided by the CIS to the American public is measured first and foremost by the public's ability to access the system. Because busy signals, long holding times, or difficulty in understanding advanced telephone prompts are unacceptable barriers to providing a responsive program, a dependable, flexible telecommunications system is the cornerstone of the CIS program. The ability to track busy signals and lost calls is essential to ensuring that at the most basic level of service there is sufficient capacity and adequate staff to handle an ever-changing call volume. The telecommunications system must offer the ability to monitor calls without the caller's perception to assist new staff in handling calls and to observe the quality of responses provided by staff.

Originally, each regional CIS office was accessed by a separate 800 number (*1*). After 1985, the Advanced 800 service enabled calls to be routed to the closest regional CIS office or to the national Publications Ordering Service from a single number: 1-800-4-CANCER. This innovation significantly improved access to the service by reducing the burden of publication calls on the regional CIS offices.

Another key program advancement was the adoption of the FTS-2000 government telephone system. The CIS was the first federal telephone information program to use it. Implemented in 1990, FTS-2000 improves user access, reduces cost, offers expanded voice and data capabilities, and is accessible from outside FTS-2000. Features of interest to local offices include equal distribution of calls among telephone stations, call attempt profiles, recorded-announcement options, management-information reports, voice processing, and direct data transfer. The call attempt profile provides a summary of calls by time of day; this is particularly useful for analyzing busy-signal rates and call volume, thereby facilitating staff scheduling.

*See "Notes" section following "References."

Management-information reports provide data on the number of calls answered or attempted, busy signals encountered by users, hold times, and average length of calls. Management reports can be generated hourly, daily, weekly, monthly, or quarterly.

At the national level, the system can route calls by area code or exchange to assigned offices. Routing patterns can be changed with minimal notice to specify time of day, day of week, and automatic rollover to another office.

By 1993, each regional CIS office will also have an AT&T DEFINITY telephone system which will bring additional technological advances, service linkages, and cost containment.

ACCESS TO ACCURATE, UP-TO-DATE INFORMATION

The primary role of the CIS telephone service is the timely dissemination of accurate, up-to-date information on the prevention, detection, diagnosis, and treatment of cancer. The use of dated or inaccurate information compromises the integrity of the program. The breadth and changing nature of the information adds to the challenge of ensuring accuracy and requires a retrieval system that is quick and easily updated. Additionally, the decentralization of the CIS program requires a system that ensures consistency across all offices and is easy to use by staff coming from diverse backgrounds.

Historically, the CIS has relied heavily on NCI publications and reports as its primary source of information. These materials are supplemented with textbooks and subject-matter files that include a variety of resources such as journal articles, internal memoranda, and news reports. Although national policies and procedures outlining the specific texts and journals to be used provide at least a minimal level of standardization, there is still variation in the resources used to respond to calls. Additionally, responsibility for updating the information resources has been left largely to the individual regional offices. Although NCI has provided the offices with routine weekly mailings to update their information resources, the frequency and methods for updating varies across the national network.

The single most significant advancement toward improving the quality of information provided by the CIS was the development of NCI's Physician Data Query (PDQ) database. PDQ is a physician-reviewed database containing state-of-the-art cancer-treatment information, listings of NCI-supported or -approved clinical trials, and directories of physicians and medical institutions treating cancer. The CIS quickly became one of the largest users of PDQ after the database was introduced in 1984 (2). Soon, PDQ became the CIS's primary resource for inquiries on cancer treatment. In 1990, to improve access and reduce CIS costs associated with searching the PDQ database online, NCI purchased uniform IBM-compatible personal computers (PCs) with CD-ROM technology and associated software. During the first year of use, the CIS staff

influenced major reconfigurations of the vendor's software to make the CD-ROM access more responsive to the needs of CIS callers. In most CIS offices, the CD-ROM is used on one or two PCs dedicated for that use. Local area network (LAN) systems, however, have been used successfully by the CIS offices at the Penrose Hospital in Colorado and the Fox Chase Cancer Center in Pennsylvania to eliminate the need for dedicated computers for PDQ access.

Another innovation that improved information quality was the introduction of electronic mail to apprise the CIS network of fast-breaking news stories. Until 1984, NCI used a manual system for informing offices: the standard telephone calling tree. Whenever a cancer-related story that might generate calls to the CIS broke, NCI would call one office, that office would call five more, and so on until all offices received the information. This procedure was time consuming and unreliable. The advent of electronic mail in 1984 allowed NCI to inform all network offices simultaneously with one consistent message.

More recent technology in national computer networks, such as INTERNET, bears exploring for downloading NCI-produced fact sheets, PDQ, etc., directly to regional offices to save time and mailing costs. The networks could also facilitate timed release of embargoed information from INTERNET into regional offices on prearranged dates.

Equally critical to the quality and timeliness of CIS information is the appropriate and consistent retrieval of that information. The CIS program is decentralized in structure. It currently consists of 19 regional offices. Together these offices employ over 200 information specialists who must access and relay information in a consistent manner. Over the years, both NCI and regional offices independently have developed a large variety of separate indexing and retrieval systems, both manual and computerized, with some using flow charts and Rolodex cards, and others using menus or keywords, to access databases. These systems direct information specialists to the most appropriate resource for specific inquiries.

Although many CIS offices retain paper-based systems (despite slowness and difficulties in updating), several offices have developed sophisticated computer-based information retrieval systems. The variety of custom-designed information retrieval systems is largely the result of the individual vision of local offices and the availability of local resources to support these systems. Hardware to support these systems includes mainframes, minicomputers, PCs for individual telephone stations, and LANs.

There has been no national standardization of retrieval systems, but the network offices have been encouraged to share resources whenever possible. This collaboration is exemplified by the Tennessee "CIS System," developed by the CIS at the Thompson Cancer Survival Center in Knoxville, Tennessee. A PC-based program, the CIS System's foundation was a custom minicomputer database developed by the CIS at the Fred Hutchinson Cancer Research Center, which was, in turn, originally based on the information and referral software application of the

King County Crisis Clinic/Community Information Line in Seattle, Washington. These are "finger-pointer" systems, which identify the appropriate pamphlets, fact sheets, and so forth (with titles, dates, sources, and annotations) in the paper collections. The system deliberately does not store specific information contained in the resources online due to the quantity of new information and revisions coming to the CIS offices each week. User-friendly menus offer a choice of information on cancer sites, community resources, and policies and procedures. A dictionary with more than 1300 terms is provided. A second system was more recently developed by the CIS office at the Yale Comprehensive Cancer Center in Connecticut and uses FoxBASE+ software for MacIntosh. It builds on a manual Rolodex system used at that and other offices. A computerized card-catalog system, it classifies references for specific inquiries in the order recommended for use. Finally, the CIS at the UCLA Jonsson Comprehensive Cancer Center in Los Angeles is investigating the possibility of adapting the Los Angeles INFOLINE service for CIS use. This computer application is unique in its ability not only to direct the information specialists to the appropriate resource but also to integrate the completion of the Call Record Form (CRF) online by storing data automatically based on the information retrieved. For example, if the information specialist enters the cancer-site menu and requests information on prostate cancer, the system automatically documents the fact that the call concerned prostate cancer.

Although the CIS has benefited from the innovation offered through these systems, many are custom-designed, limiting their adoption outside the CIS office that developed them. When developing nationally standard information and reporting software applications, however, "bridge" software to existing, cost-effective custom programs should be examined for cost savings in integrating current and future applications. Benefits and drawbacks of non-finger-pointing retrieval systems (which can also store the thousands of pages of the resource texts) also need to be explored, particularly in light of the newer technologies of split screens and text scanners. (These technologies mean that an information specialist could review an article on one part of the computer screen while searching for community resources on another part. Text scanners transmit print material directly into computer databases.) LANs within regional offices and wide area networks (WANs) nationally should be explored to provide more effective use of the PDQ CD-ROM technology and other computerized resources. It will be important to position the CIS with regard to existing national and regional networks and electronic bulletin boards (such as INTERNET as well as the National Library of Medicine's regional projects and the federal government's National Research and Education Network as discussed in the High-Performance Computing Act of 1991). This positioning for future links will ensure greater access for the public and health professionals for gathering and sharing CIS information and for community outreach activities. For example, the CIS at Penrose Hospital in Colorado is

linked with Integrated Medical Systems, a statewide network of physicians, hospitals, pharmacies, and other organizations for transmitting text, medical images, and voice messages.

DEVELOPMENT AND USE OF COMMUNITY RESOURCE DIRECTORIES

By contract, each CIS regional office must collect and update information on 12 categories of community resources, including hospice, home health care, transportation, and support group services in its service area. These directories are large, often including thousands of entries for a single service area.

Computerization of these directories is another appropriate application of information-management technology to the CIS. It is a popular application in the CIS system, second only to computerized storage of CIS call data. Several offices that have developed computer-based resource directories have found that they increase the accuracy and efficiency of providing referrals. Currently there are seven such systems in use network-wide that rely on five different software programs: MUMPS, PARADOX, RBASE, FOLIOS, and DBASE IV.

One of the most comprehensive systems is the Community Resource Directory database of the CIS at the M. D. Anderson Cancer Center which is integrated with the Texas Cancer Data Center (TCDC) database. The Community Resource Directory database contains community resources cataloged by county and type of service. In addition to the services required by NCI, files in the TCDC database include tumor registers, population data, cancer mortality data, and community profiles. Individuals may obtain information from the database by contacting the CIS or by modem through TELNET or TEXNET. This system is accessed regularly by more than 1700 registered users, including physicians, discharge planners, social workers, librarians, and program planners.

Community collaboration has occurred in other systems as well, including the Cancer Resource Directory Coalition (CRDC) project in New York and New Jersey (linked with the CIS office at the Memorial Sloan-Kettering Cancer Center) and the New England Cancer Resource Directory (developed at the CIS at the Dana-Farber Cancer Institute in Boston). The CRDC's 26 cancer-related agencies developed a database to provide resource information that could be disseminated through print and electronic media, including LAN networks. The New England Cancer Resource Directory is a regional computerized resource directory indexed by state. Annual updates in coordination with statewide umbrella organizations result in printouts that are shared with a variety of local agencies.

Maintenance of the various regional paper-based and computer-based systems can be time consuming and costly. There is no consistency in the specific content, and with some exceptions, the utility of the computer systems is limited to the CIS.

A nationally developed computer database with regional community-service data updates would provide the consistency necessary across the CIS network and provide ready access to uniformly formatted data by national staff. Although the initial start-up costs would be significant, NCI would save costs currently incurred to support offices with separate computer systems and, more importantly, the higher costs of the offices still using manual systems—a majority. Again, bridge software should be explored as one way of meeting national standards while allowing previously developed local custom software that is cost effective to continue. A nationally developed system could benefit not only the CIS but also all of NCI and other organizations such as the American Cancer Society (ACS) and the Centers for Disease Control and Prevention (CDC). The NCI should consider collaboration with ACS and CDC in the development of a common system which would keep all three organizations abreast of the community resources provided by the others. As with other information-management systems for the CIS, links to established national electronic networks and bulletin boards should be explored.

PROGRAM MANAGEMENT

Effective management of the CIS program requires a strong internal communication system that facilitates rapid and easy communication between NCI and the regional offices and among regional offices. The advent of network electronic mail revolutionized program communications in the 1980s and provided for rapid transmittal of technical and media updates from NCI to regional CIS offices.

Currently, the CIS uses AT&T Mail as part of the FTS-2000 telecommunications service. Features include confidential messages, on-line directory of system users, mailboxes keyed to various types of information (i.e., priority meetings), and custom lists for simultaneous messages to selected groups (*see* CIS task forces described below). One drawback of AT&T Mail is that a modem must be used to access the system to check periodically for messages. Use of electronic mail within CIS parent institutions is growing as well. Voice-mail is used in many offices, facilitating the relay of messages.

The XMODEM protocol is part of the AT&T FTS-2000 system used by all offices. It interfaces with electronic mail at each of the CIS PDQ computer work stations and enables transmission of letter-quality documents by uploading and downloading WordPerfect documents from disk. This has reduced the network's reliance on more expensive overnight courier services.

Facsimile machine access is available in all offices. Its use increases the speed by which local materials can be reviewed and approved by the national program staff and reduces reliance on overnight mail services.

The CIS program uses a variety of task forces to assist in the management of the CIS network. These task forces and target-audience working groups deal with a variety of

issues such as the development of policies and procedures, evaluation of the CIS program, and outreach to specific target audiences in the community. Because membership includes representatives from across the CIS network, routine meetings are difficult and prohibitively expensive. As a result, task forces frequently substitute conference calls for meetings. Although useful, conference calls are time consuming and are often of marginal sound quality. Software that facilitates on-line discussions could take the place of or provide a useful supplement to task force conference calls.

Management of the network could be improved through the use of an electronic bulletin board system or an electronic mail system with more advanced features: closer integration with regional office computer systems to provide immediate notice of messages received or sent and to facilitate on-line discussions at various networked computers within regional offices.

COMMUNITY OUTREACH

The strength of the CIS outreach program depends heavily on the ability of the CIS to capitalize on its decentralized structure. The CIS program has the unique ability to provide local input into national outreach programs based on knowledge of the service area and to target national education programs to specific high-risk populations. This, however, requires access to a variety of local data and the ability to interpret and use the data for specific programs. The data must be accurate, up to date, and unique to the service area.

Currently, the CIS relies on local census data and cancer registry data, where it exists. The Office of Cancer Communications (OCC) hopes to offer the regional CIS offices a unique supplement to this information through the use of the INFORUM database. INFORUM combines census data with marketing information, which can be adapted for OCC education initiatives. For example, specific information on the location and use of mammography facilities could be added to assist in targeting education interventions in specific communities. OCC hopes to be able to provide each CIS office with a profile of its region to assist in outreach program planning.

Computer applications also are being used for tracking intermediary and media contacts, outreach materials development, communications, and documentary activities for reporting requirements and management review. Many offices use either commercial or custom software programs for storing information on intermediaries and media contacts. One such commercial program is TELEMAGIC, which allows systematic monitoring of intermediary contacts and offers a mail-merge feature for automatic label generation. A custom publicity and promotion program was developed on "Advanced Revelation" software by the CIS at the Fred Hutchinson Cancer Research Center to track media and intermediary contacts, facilitate collaboration, and disseminate promotional materials. Thirty-three index categories organize in-

formation on contacts, including a chronology of past collaborations and links to a mail-merge program. The CIS at the Fox Chase Cancer Center has also developed an outreach database using ORACLE and RBASE software for targeted-marketing purposes.

As OCC increasingly stresses the networking function of the CIS outreach program across the new, larger regions, the need increases for inexpensive and timely ways to disseminate and localize educational and promotional materials. Production of tailored materials has been greatly facilitated by the uniform use of WordPerfect software across the CIS network. Graphics software, scanners (which read text directly into computers from any printed material), literacy evaluation software, translation programs, and computerized slide production are increasingly used. They speed the development of printed materials, attractive overhead and slide presentations, and training materials for the outreach area. Increasingly, media and intermediaries are requesting that publicity and promotion materials be on computer disk rather than in hard copy. Linking CIS offices to existing news electronic networks would allow for electronic distribution of public service announcements from the CIS regional office computers as soon as NCI sent materials.

As the CIS outreach staff becomes larger and more dispersed, hardware such as pen-based technology and portable computers (laptops, palmtops) will enable the CIS outreach staff in the field to record and transmit information back to the main office for immediate use in planning and program evaluation, and links to regional and national computer networks will facilitate dialog with intermediaries.

The national and field offices are also exploring the development of a computerized outreach activity documentation system to provide institutional memory, documented accountability for goals, and information-management review and prioritizing of tasks. This exploration should include a review of existing marketing software tools as well as tools used in other health-education applications (e.g., Health Education Resource Management System [HERMS] used nationwide by the Indian Health Service).

TRAINING

Effective staff training and continuing education are the foundations of a high-quality program. Mechanisms to provide consistent, accurate, and up-to-date training network-wide are essential. Currently, the content and style of training programs for both the phone service and outreach are the responsibility of the regional offices, but the addition of a national staff person to develop training programs promises to add more consistency to the CIS's training capabilities. The emerging use of interactive video disk technology offers significant training opportunities for both the phone service staff and the outreach coordinators and should be explored by CIS program staff. (This technology is used by police, public school teachers, and patients. The Foundation for Informed Medical Decision

Making in Hanover, New Hampshire, recently released an interactive video on breast-cancer treatment choices, with consultation from Dartmouth University).

QUALITY ASSURANCE

Monitoring of responses in an objective manner that allows the program staff to identify training needs and react to individual problems is essential. The Cancer Information Service Telephone Evaluation Reporting System (CISTERS) national test-call system described by Kessler et al. (3), illustrates an innovative use of computer technology for quality assurance; CISTERS may have significant implications for training and resource development. National standardization of information retrieval is crucial to this process.

PROGRAM EVALUATION

The ability to track and document CIS activities is critical. Documenting inquiries to the CIS assists in evaluating the effectiveness of NCI education initiatives and provides direction for the development of new initiatives and patient-education materials. The system for capturing this information must be consistent and reliable within offices and between offices. It also must be flexible and allow for easy changes to capture public response to fast-breaking news stories. The transmission and analysis of the data must be rapid and must allow NCI program staff to respond immediately to questions from the media and Congress. Frequently, their questions address the ability of the CIS to respond to specific programming or the needs of individual constituencies.

Although many offices began collecting data on calls in the late 1970s, standardized data collection did not begin until 1983. Since that time, more than 4 million CRFs have been entered into the CIS database, providing a wealth of information on CIS users and information-seeking trends.

In their book *Searching for Health Information: The Cancer Information Service Model*, Freimuth, Stein, and Kean discuss the importance of the information collected and coded on each call (4). Variables include staff identification, case number, and cancer site as well as topic of inquiry, behavioral suggestions, user demographics, and time to handle the call. Data generation is a four-step process: manual completion and coding of the CRF, data entry into a local office computer system, data cleaning and management (change for out-of-range entries and internal coding inconsistencies), and report generation. Problems encountered in the network have included differences between CIS offices in interpretation of the coding variables, data collection and timeliness of data entry, and variations in the programs used for data entry and cleaning. The hardware systems supporting the data-collection activity at the local offices include mainframes, PCs, and minicomputers. Tapes or disks are forwarded to NCI for aggregate analysis.

The data-collection function would benefit tremendously from standardization. Coding could be streamlined and accuracy enhanced by the adoption of a computerized CRF. The national CIS, which, prior to 1993, served areas of the country not served by local offices, developed an electronic CRF in 1987. Although innovative, this system was custom designed and may prove difficult to manage and service on a network-wide basis. Minimally, standardized data-entry programs that limit out-of-range entries and internal inconsistencies in coding would facilitate the data-cleaning process and improve the quality and consistency of the data. A recent effort to transmit data via BITNET should eliminate the need to transfer the data from the tape format and should speed analysis. Using scanning technology to input CRFs directly over modem lines into a database will also be explored for cost savings.

DISCUSSION

The promise of current and emerging advancements in telecommunications and computerized information management hold a dramatic potential for improving the operation of the CIS. Although initial start-up costs would be considerable, the potential cost savings and significant improvement in quality of service warrants the commitment of staff and resources to develop and implement a strategic approach for computerization of the CIS program.

The development of this strategic approach should include the following:

- Assessing all program areas that could benefit from nationally coordinated and developed computer applications.
- Surveying all current custom applications in the network.
- Prioritizing the needs by potential benefit and cost. Examining consistency and quality to determine which applications should be network-wide and which should be customized for individual offices (perhaps using bridge software to connect with current, independently developed applications).
- Surveying computer applications from NCI, the National Institutes of Health, and commercial and nonprofit sources that would apply to the CIS.
- Ensuring that the CIS network staff (administration, telephone service, and outreach) have input throughout the entire process (possibly through a separate technology task force).
- Ensuring that the most current level of technological expertise from profit and nonprofit arenas is used for coordination and consultation.
- Ensuring coordination with ACS and CDC for common database needs.
- Ensuring that recommendations for LAN and WAN applications will position the CIS national program to link

with 1) developing national networks (such as the National Research and Education Network mandated under the High-Performance Computing Act of 1991 and the regional networks of the National Library of Medicine), 2) any future government-supported limited universal network access for poor and rural users, and 3) existing media and marketing electronic networks.

OCC also needs to assess the infrastructure (staff and resources) needed to support this computerization. In addition to hardware and software, resources for staff to coordinate the initial introduction of the technology, for training network staff, and for updating and maintaining the systems selected need to be considered.

Although it will require a significant commitment of funds by NCI, integration of nationally standardized state-of-the-art telecommunications and information-management technology not only will enhance CIS program operations but also will increase the flow of information to the public; that flow of information is the primary purpose of the CIS. As the CIS program prepares for the most significant structural change in its 15-year history, there should be no delay in the adaptation of technology that will allow the program to reach its full potential.

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The First 15 Years: What Has Been Learned About the Cancer Information Service and the Implications for the Future

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The Cancer Information Service (CIS) has been in existence for over 15 years. During that period, lessons have been learned that have been used to increase the effectiveness of the network. This paper lists 12 of those lessons, covering issues such as giving sophisticated medical information; reaching diverse target audiences; using the mass media; developing systems needed for quality assurance, research, and information technology; and nurturing a local-national partnership. The paper also discusses major accomplishments of the program and lists recommendations for meeting the challenges to be faced by the CIS in the future. [Monogr Natl Cancer Inst 14:177-185, 1993]

The vision of the early architects of the Cancer Information Service (CIS)—to bridge the gap between cancer research and community practice by giving the public direct access to accurate, up-to-date information on cancer—has been achieved. One of the longest-running community programs in the National Institutes of Health, the CIS has been closely scrutinized, monitored, modified, and improved.

As the papers in this special monograph have noted, the CIS faces a myriad of new opportunities as well as fresh challenges as a result of its latest reconfiguration into 19 regional offices covering the entire country. This paper will delineate the major accomplishments of the service, examine the lessons that have been learned by the CIS during the past 15 years, and describe the implications of these lessons for the CIS in the 21st century.

MAJOR ACCOMPLISHMENTS

The many accomplishments of the CIS include the following:

- The CIS, one of the longest-running community-service programs of the National Cancer Institute (NCI), has taken over 5 million calls.
- The CIS is one of the most heavily used health-related telephone lines in the country.
- Using a standard Call Record Form, the CIS has consistently recorded data on calls since 1983, building a dataset of over 4.25 million calls.
- The CIS has established a viable structure for operating a high-quality service.
- The CIS has proven that it is a dynamic entity, with the ability to disseminate quality information quickly to meet changing national priorities and needs.

- The CIS has established a means of creating and maintaining relationships and boundaries with diverse national partners, such as the American Cancer Society and other voluntary health agencies, the comprehensive cancer centers, and the American Association of Retired Persons.

- The CIS has forged definitive protocols for numerous aspects of its operation, such as training information specialists, structuring test calls, and instilling policies and procedures.

- The CIS has been quick to introduce technological innovations that have improved the service.

- The CIS, through the Office of Cancer Communications (OCC), has been a pioneer in the nonprofit health field in trying modern media methods, such as video news releases and satellite media tours. The expertise gained by OCC in this essential element of the CIS sets a standard for other health communications programs.

- CIS users are satisfied with the service. Surveys show that 94% of respondents are satisfied with their overall use of the CIS.

- The CIS has shown, through a limited amount of research, that a rich potential exists for testing the efficacy of new strategies.

- The CIS has served as the model program for other information services in this country as well as in other countries. Today there are over 22 similar services in Europe.

LESSONS LEARNED AND FUTURE CHALLENGES

Many lessons have been learned in the years the service has been in operation. Twelve of these lessons are discussed below.

1) It is possible for well-trained information specialists to give sophisticated medical information on cancer to patients and family members over the telephone.

Several studies, some reported in this monograph, verify the fact that the CIS has been able to fulfill the task of giving complex, accurate information on cancer to patients, their family, and friends. As noted in the article by Manfredi et al. (1), a majority of patients and family members who made treatment- or care-related decisions

*See "Notes" section following "References."

aided by information from the CIS felt "more knowledgeable, more able to understand and discuss with the physicians the options available to them, and more confident of having explored all options and chosen the best one" (p. 101). The training provided to help CIS information specialists respond more fully to callers from the lay public has paid off. The CIS is providing accurate, objective information to patients and their families, allowing them to make more informed decisions.

Manfredi et al. concluded that the information specialists "must have skills to meet the needs of patients with high anxiety levels, they must have access to the most current cancer knowledge, and they must be able to communicate this type of information clearly. The high level of satisfaction with the CIS reported by most callers in this study suggests that the CIS staff are meeting these requirements" (p. 103). This critical service and the sensitive manner in which information is being provided to cancer patients and their relatives and friends during a crucial time are a tribute to both NCI and the CIS.

The patients who call the CIS tend to be more ill and more stressed by their illness than cancer patients who do not call the CIS (1). This fact emphasizes that the CIS is playing a critical role by responding to those in greatest need. It also highlights the need for specialized training for the CIS information specialists who face formidable and difficult challenges on a routine basis every day. The training method that has been used—training the CIS supervisors who in turn conduct local sessions for the information specialists at their own offices—has proven to be a wise and effective choice.

The challenges for the future will be to reach a broader spectrum, representing more of a cross section of the population. One group that needs to be targeted is older patients (2). They are more likely to be treated at smaller hospitals where they are less likely to receive more than one type of treatment or be referred for oncologic consultations; they receive less aggressive treatment; and they are less likely to be referred to clinical trials (3). Economically and educationally deprived patients, who are at greater risk for cancer and whose cancer is usually found at a more advanced stage, are another important group to address (4).

The CIS in the future will need to find a way to continue to offer high-quality service but also to communicate to an ever-diverse population. Its Training Task Force needs to concentrate on structuring methods to teach skills needed by the information specialists to present complex medical information to this diverse audience.

2) It is possible, using information sharing over the telephone, to influence or change behavior of callers and their caregivers at critical decision-making points.

The data show that the CIS can influence behavior in the important target group (5) of patients, family members, and friends. Altman (6) revealed that 75% of CIS callers who had cancer-related symptoms at the time of their calls, but who were not yet diagnosed, made contact with a health professional after calling the CIS. Only 50%

report that they definitely would have made contact with a health professional on their own initiative (i.e., without calling the CIS). The study was the first to document this potential value of the CIS in encouraging sound health behavior in symptomatic callers nationwide.

The study by Manfredi et al. (1) also suggests that information communicated by the CIS to cancer patients and relatives may indeed influence clinical decisions. A high percentage of these callers (51%) took at least one of three actions as a result of their CIS contact: 42% discussed information received from the CIS with their physicians; 18% made contact with the referral given or with the referred physicians/institutions associated with clinical trials; 27% discussed the Physician Data Query (PDQ) printout with their physicians. An even more direct impact on treatment decisions was evidenced by the 12% who reported that the CIS information helped them to find a new physician or led them to a second opinion and the 10% who used the information to help decide for or against a specific treatment.

Manfredi et al. (1) indicate that there is a significant potential in the CIS for technology transfer—of clinical research directly to the patient and of information provided by patients to physicians. Nearly 20% of patients reported that their physicians asked for more information or consulted another physician or other source about the information provided to CIS callers.

Another paper in this monograph, by Crosson et al. (7), gives evidence of the same kind of technology transfer, with a dramatic increase in enrollment in clinical trials following a special training program for the CIS and a change in CIS policy for dissemination of clinical trials information directly to patients calling the network. Last year, over 95 000 referrals were made by the CIS to clinical trials and cancer centers (8).

Future challenges include a need to look more closely at the behavioral influences of the CIS with these target groups, including medical studies of the transfer of CIS information directly to patients, by patients to physicians, or to patients from physicians. The research needs to confirm that such transfer occurs and to assess how it affects clinical decisions. In addition, further studies need to identify the information needs of minority patients and their relatives.

3) Women use the CIS more than men do, just as they make other health-care decisions more often than men do.

Since the beginning, more than 70% of the callers to the CIS have been women, far exceeding the percentage of females in the general population. A question that has been raised in this monograph is whether this is a problem that needs correcting.

When one looks at the role of women as consumers in the health field, the problem is not as serious as one might think. Indeed, hospital marketing specialists understand that not only are women the major users of health-care services (of 20 common operations, 11 are done exclusively on women) but they also are responsible for the

majority of health-care purchasing decisions. Women are the gatekeepers of health information both for themselves and for their families. They make an estimated 80% to 90% of all family and health-care decisions and spend an estimated 2 of every 3 health-care dollars (9).

Among specific selections they make for themselves and their families are the following (10):

- Women choose the hospital for treatment of illness or injury six out of 10 times.
- Women are four times more likely than men to select a health-care provider for treatment of a child.
- Women select physicians almost twice as often as do men. Surveys indicate that women choose 53% of the regular physicians used by their families, and men choose only 28%.
- Women are more likely to have a chronic illness needing regular care. Eighty-three percent of women (compared with 73% of men) regularly go to the same physician.

Manfredi et al. (1) found that among their comparison sample of cancer patients, those who did not seek information were most likely to be male. In addition, cancer patients whose relatives called the CIS (rather than the patients making the call themselves) were more likely to be male.

Studies of care given to cancer patients cared for at home (11) find that approximately two thirds of the caregivers are females. Caregivers are usually wives, daughters, or daughters-in-law. To provide care for relatives, women are more likely than men to work reduced hours, to rearrange work schedules, to take off time without pay, or to leave their jobs. Economically deprived women bear an even heavier burden in the area of caregiving at home than do women with higher incomes.

Rather than questioning the heavy volume of calls from females, the CIS should use it to its advantage. The evidence seems clear that women should be an important target group for many of the CIS services and that it is a group that should get even greater attention.

Conversely, the CIS has shown that it is possible to attract male callers for specific issues. For instance, during Prostate Cancer Awareness Weeks in September 1989 and September 1990, when the CIS number was publicized as the information source for free prostate-screening examinations, the majority of callers seeking that information were male (67% in 1989 and 72% in 1990).

The challenge for the future will be to encourage more types of people to call the CIS—targeting the underserved women in the country, reaching the older women, those of diverse ethnic backgrounds, and those with less education, as well as males over 50, blue-collar workers who smoke, males living alone, and economically disadvantaged males.

4) A major target audience in the area of cancer prevention—smokers—can be reached and helped through a telephone information service.

Two factors have worked together to achieve success in the area of smoking cessation. The first is the collabora-

tion of NCI with the Office of Smoking and Health of the Centers for Disease Control and Prevention in the production and distribution of motivational public service announcements (PSAs) promoting the CIS number (12). This joint promotional effort has produced PSAs that reached a large proportion of the population of the country. These PSAs have been effective in encouraging people to take an important first step in trying to quit smoking—calling the CIS (13).

The second factor was the decision by NCI in 1987 to train the network in counseling smokers, using the scientifically based stages of change (precontemplation, contemplation, action, maintenance, and relapse) (14) to fashion a protocol that can be tailored to each caller.

There is no doubt that smoking is the single most preventable cause of premature death in this nation. During the past 15 years, the CIS has received more than 413 000 smoking-related calls and has provided at least a first step in the quitting process for many of those callers.

There are several recommendations for future work in this area.

One of the barriers to smoking cessation is the smoker's lack of access to help when he or she is ready to take any of the major steps toward quitting. The CIS offers several opportunities for removing this barrier and for improving the quitting rate. It is available for the smoker to call whenever he or she is ready. It has personnel trained to help. Further contacts can offer an easy and affordable source of ongoing encouragement for smokers who want to quit. The CIS can be a force in helping former smokers avoid relapse (the vast majority of smokers who try to quit fail in the first month). The CIS needs to determine some effective strategies for using the initial contact from smokers to provide necessary assistance to prevent relapse. If it could become more active in this area, the CIS could aid in the effort to make the prevalence of smoking in the United States decline more rapidly than it currently is.

The CIS also needs to incorporate programs to reach specific target groups of smokers, such as mothers with children in the home (15); to find effective ways to reach other high-risk groups of callers, such as men and blue-collar workers; and to test the effectiveness of its interactions with smokers (16).

There are probably other areas in cancer prevention, such as nutrition, where a telephone information service can make an important difference. The CIS needs to examine these areas carefully to determine if counseling protocols on certain aspects can make a similar impact on other high-risk behaviors.

5) Targeted, hard-to-reach audiences can be reached by the CIS, providing a needed service to these groups.

In the past 2 years, NCI has chosen, based on national priorities, four major groups to target in national initiatives—older Americans, Hispanics, African Americans, and persons of low literacy. Local CIS office outreach personnel, along with the telephone service staff, are concentrating on reaching one or more of these audi-

ences. Although calls to the CIS are only a surrogate measure of the success of this program, the new emphasis on reaching these disadvantaged audiences is beginning to pay off.

In the older Americans group, for example, the percentage of calls to the CIS rose both in 1990 and in 1991, and the older Americans who called were seeking information on essential subjects, such as where to obtain mammograms, treatment, and hospital/physician referrals (2).

The 1991 NCI promotional campaign for National Minority Cancer Awareness Week used culturally sensitive themes and artwork to promote the CIS to minority audiences. Calls from African Americans in the California CIS office, which normally receives about 9% of its calls from this target group, rose to 26% during this period (12).

In addition, Freimuth's study (17) found that the CIS information specialists are able to provide information to non-White callers—97% of the African American callers to the CIS were quite well satisfied with their experience, feeling that the information specialist was understanding, encouraging, caring, supportive, and polite. Ward et al. (18) examined CIS call data for specific subjects (risk factors, smoking, breast cancer, and publications). They found that the information specialists spent more time on the telephone with ethnic callers (Asians or Pacific Islanders, Hispanics, Native Americans, and African Americans) than they did with White callers. As noted by both Freimuth (17) and Ward et al. (18), however, minority audiences that respond to CIS media campaigns tend to be similar in educational attainment to Whites who respond.

There are many challenges for the future in this area. Although this evidence shows that the CIS can effectively service these groups, much work must still be done to reach these specialized audiences. The addition of outreach personnel in the local offices and the strategy of using intermediary groups (such as churches) known to the specific target groups to reach into the specific communities should help to increase the ability of the CIS to make advances in this area. The outreach component furnishes significant opportunity for conducting research that will help to identify those models with the most potential for replication 1) that reach and serve specific groups and 2) that use the CIS as a link to other intermediaries who serve target groups.

In addition, innovative strategies will be needed to motivate calls from specific subgroups, such as minorities, those with less formal education, and those with lower incomes, and all three of these subgroups in the older age category. A better understanding also is necessary of how to reach those selected audiences that still remain at high risk for cancer. Media habits must be understood to select the appropriate channels to be used to carry cancer messages to each of these subgroups. Credible individuals must be recruited as spokespersons to carry the messages. Careful pretesting of media materials and of the credibility of media spokespersons will be essential to this endeavor. These are areas that provide fertile ground for formative research.

6) Structuring outreach in a way that strikes a delicate balance between national directives and local autonomy, while allowing for meaningful evaluation, is a distinct challenge.

Early CIS contracts gave broad responsibilities to local offices for outreach programs, which were carried out in a diverse fashion with little national direction (8). Increased national direction was added as NCI's OCC programs became more specific.

Many of the past outreach efforts were successful in their own right. Because the projects were diverse, however, they did not have common objectives that could be articulated and directly related to NCI's national priorities. Moreover, because of the kind of activities involved, many did not include rigorous evaluation components. The Partners in Prevention effort seems to have come closest to fashioning a nationwide program, based on the strengths of the CIS as a major NCI intermediary. It was well planned, with local input. It was phased over several years. It had a broad set of specific, integrated projects and activities for local CIS offices to complete. Regional workshops brought together local constituencies that had been identified by national counterparts who were also involved. Unfortunately, before the program could show any measurable impact, the local staff leading the effort were deleted from the contracts.

The restructuring of the CIS regions and the addition of a major outreach component in the new offices have created a new opportunity for the CIS outreach program to help the NCI reach its national priorities and audiences. To make the most of this new opportunity, however, several factors will need to be present: 1) a joining of the best minds, both at the local and the national levels, to forge a cooperative program that has a chance for success; 2) an agreement from both levels to try a narrowed, more directive structure; 3) an identification of intermediaries with national commitment and a local constituency ready to work; 4) a time frame that is long enough to measure change; 5) evaluation mechanisms in place that are clearly defined and able to detect subtle changes; and 6) a commitment to research to aid in answering the many questions that are already on the table.

7) A partnership, using the strong media skills of the national OCC, paired with the reality testing available at the local level, can produce effective promotion campaigns.

The media has played a starring role in the success of the CIS. From its earliest inception, the CIS has used national media plans, each one identifying specific needs and priorities and assigning respective tasks for national and local promotions. These media plans have produced impressive results (12).

Although the mass media has demonstrated the fact that it can influence the number and types of calls as well as the type of callers, a full complement of strategies and materials is necessary to reach specific groups of people and to sustain their calling. This package approach in-

cludes a mix of PSAs, message and story placement, planned news events, and seizing the opportunity created by unplanned news events. The new world of program-length commercials, talk shows, MTV, and interactive computer information services needs to be explored.

Future challenges include the need for a long-range national promotion plan, built tightly around NCI target audiences and priorities, defining criteria for choosing national intermediaries and constituencies, and supporting CIS planning decisions. The plan must be framed to increase the specific kinds of callers and types of requests described earlier in this article. Roles and responsibilities for the national and local offices, including the integration of the outreach component, need to be re-established, redefined, and included in the plan.

The use of formative research, including the pretesting of strategies and the use of spokespersons and messages for reaching the specified audiences, also needs to be articulated in this national plan. The process that worked in the past, with the Promotion and Outreach Task Force involved in the development and coordination of the plan, should be used to ensure that regional needs are met and that local implementation will occur to support the national promotion efforts.

The issue of paid advertising needs to be more thoroughly studied, its effects must be compared with full promotion campaigns, and a funding mechanism for its added expense must be determined before recommendations to make it part of the program are made. Public-private initiatives may offer an untapped potential that could be used to augment resources available to OCC for its promotion activities, as well as for outreach activities, such as establishing or strengthening coalitions and developing and distributing materials. NCI has had several productive relationships with private-sector organizations (12). Clearly defined policies and procedures for judging such relationships must be put in place, however, along with sound planning strategies, before any programs can be initiated with new public-private partnerships.

8) A national quality-assurance system is feasible, acceptable, and necessary to ensure a high level of consistency and service.

Throughout its history, many attempts have been made, both at the national and local levels, to assess the quality of the CIS. Working together, through the CIS Evaluation Task Force, several quality-control measures have been added to the service over the years, including initial and continuing staff training, approved policies and procedures, the network-wide availability of state-of-the-art cancer information, and local and national monitoring systems. Evaluation of the service, using comparable data to provide a technical base, has proved invaluable at both levels for program management and for sharing the CIS experience with others in a more objective and useful manner.

The new Cancer Information Service Telephone Evaluation and Reporting System (CISTERS) (19) provides an essential step in the ever-evolving quality-assurance pro-

gram. This national model, using a computer-based, interactive interviewing system to measure continually the quality of the service with objective, statistically valid, reliable instruments, is a unique resource. CISTERS also provides a vehicle at the national level for technology transfer, assembling current information on the CIS as a whole that can be fed back into the management and training aspects of the program, identifying resource needs, and gathering information that NCI can use in directing other CIS and OCC projects.

The importance of quality assurance and evaluation for any program of this type, scope, and cost cannot be overstated. It is clear that NCI has the ethical responsibility to ensure that the sensitive medical information being given by its local partners is of the highest quality—consistent, accurate, up to date, and delivered with compassion. On the other hand, each local office has an equal stake in quality assurance, needing to ensure that its information specialists are providing a service that meets the quality and constancy expected by its funding source. The active participation of the CIS network personnel in the planning and implementation of this newest quality-assurance component needs to be continued to add viability to CISTERS.

A future challenge will be to continue to find ways to use the data gathered by CISTERS in a positive way to improve the quality and breadth of the service. This program will increase the knowledge base of quality-control measurement nationally. NCI can lead the effort to discover means to help adapt it for use by other health-oriented information services.

9) The limited research that has been conducted on the CIS has helped to test new strategies that can improve and expand the dimensions of the program.

Although the CIS is a service program, it offers a unique resource for research. The results of the five studies funded in 1985 by NCI as part of the Cancer Communications Systems Research program initiative and reported in this monograph (5), as well as the other research conducted with little or no extramural support, are an indication of the rich potential that exists for using the CIS as a research tool.

It is somewhat surprising that during the 1980s, when the CIS was organizationally lodged in an NCI division that was shifting its priorities from outreach to research, this service—with its sheer volume of contacts with people discussing cancer-related problems and with its outreach program—was not considered a viable opportunity for control/prevention research (8).

There are several recommendations for future consideration. Complete data should be collected on each incoming CIS call. The network has been limited by a ruling of the federal Office of Management and Budget that restricts the collection of data on incoming CIS calls to 20% of the calls. Although each office has been assigned a sampling plan that makes the database representative in a generic sense and although the database as it is presently constructed represents a rich resource, there are many

difficulties with this constraint. As noted in several papers in this monograph, this data-collection restriction makes it difficult to track effectiveness of CIS promotions, especially to the targeted populations, and to judge the power of different media types and different media strategies. It limits the ability of the individual offices to judge their effectiveness in reaching specific target populations. No data are presently being collected on the persons who call the Publications Ordering Service, thus the callers seeking cancer-prevention information are not tracked. Nor have demographic data ever been collected on persons who call the CIS more than once—previous callers make up 21% of the total volume—another rich data and research opportunity.

With the strengthened and restructured CIS, many research opportunities present themselves:

- Hypothesis-testing studies, similar to the mammography study (20) that will use the occasion of the incoming CIS call to provide information that might not have been contemplated by the caller or that might be unrelated to the original question but that promotes other national priorities.

- Developmental studies that will try innovative ideas, such as outcalling to populations that do not now call the CIS.

- Behavioral studies that will test the theories of information-seeking and cancer-control behavior changes, using cue-to-action strategies.

- Systematic studies to evaluate the barriers and facilitators in targeted communities to calling the CIS and to pretest message strategies based on the results.

- Impact studies of CIS promotional campaigns within defined populations to learn who calls and why, to determine how to reach specific audiences, and to evaluate the effect of CIS promotional campaigns on those who do not call.

- Intervention studies that will carry the results of successful pilot studies to several CIS offices or to the network as a whole.

- Social marketing studies of how the CIS calls and media promotion work together or independently to influence subsequent action.

The entire issue of the extent to which CIS call volume can serve as a marker of the concerns of the population and thus can serve as an early-warning sign for population-based change is another research question that needs exploring. Of course, investigators will need to continue to be sensitive to the issues involved in conducting research in an environment where the main goal is to offer a high-quality service.

It has been shown that the CIS is a viable laboratory for behavioral and communications research. It is recommended that a plan be devised that will integrate new research and augmented data collection into the program—and that this plan be made into a national priority.

10) The adoption of the latest available technology by NCI has benefited the entire CIS network and has kept the system in the forefront.

The CIS has been a leader in adapting technological changes related to the capabilities of the telecommunica-

tions systems supporting the telephone service. It quickly used the advent of switching capacity to convert all the offices to the single 1-800-4-CANCER number. Advanced 800 service was the next innovation, and CIS management took the opportunity to create the Publications Ordering Service to siphon off simple publications requests so that the local offices could concentrate on the increasingly sophisticated questions coming their way.

Another major technological innovation was the development of NCI's PDQ system, a user-friendly computerized database that permits quick identification of state-of-the-art treatment (21). Updated on a monthly basis, PDQ provides an invaluable and efficient resource for the CIS in responding to public and professional inquiries on cancer treatment. (The CIS still accounts for more use of PDQ than any other single source.)

The critical need for NCI and regional offices to communicate regularly, particularly when urgent news about cancer appeared in the public media, prompted NCI to establish an electronic mail system that has worked well for quick communications and also for eliciting feedback on issues at hand.

This area provides a major challenge for the future. Today the CIS is a perfect candidate for the application of emerging information-management technology. Some innovations have been undertaken in some offices, but the network as a whole lags behind in this area (22). The lack of a national plan has fostered the preservation of largely paper-based information-management systems in many local CIS offices. Although the various innovations have contributed to the development of the CIS system individually, they have been sometimes duplicative in nature and piecemeal in their applications.

It is recommended that a strategic plan, developed with the input of the local offices, be devised for the introduction of this technology, including the development of the infrastructure to implement it. Several areas need to be addressed: information storage and retrieval, data processing, electronic communication, and transmission capabilities. This critical need will not only integrate the network but also will promote consistency within it.

The innovations already in place in the network and the new emerging technologies position the CIS program to develop a strategic approach to ensure a uniform and integrated information-management system that will enhance the efficiency, consistency, and productivity of the program. It is an urgent need that must be addressed in the near future.

11) The open partnership forged between the NCI CIS project office and the local CIS offices has resulted in a strong service.

The cooperative working relationship that has existed from the beginning of the CIS between the NCI CIS project office and the local offices has permitted the building of a program that not only meets national goals and objectives but also is based on the realities and difficulties of running a high-quality program in the field (23).

Though the program has changed organizationally, its mission and purpose have been unvarying. Each of the two entities operates within its own environment: The NCI project office, now located within OCC, must deal with the environs of the institute and of the National Institutes of Health and with national constituencies, such as the Congress, as well as major national agencies and institutions; the local CIS offices, on the other hand, must operate within their own sponsoring institutions, often comprehensive cancer centers or major medical centers with significant commitment to the cancer problem. In their local service areas, these offices must also build relationships with other cancer-related organizations, such as state health departments, American Cancer Society divisions, and NCI-sponsored grantees. The natural tension that arises from working in so many different environments has produced a positive effect on the CIS program. It has fostered a lively exchange that has helped the CIS adapt to many changing conditions over the long history of the program. It has found ways to deal with conflict when alternative views occur.

The CIS also has had key leaders, both at NCI and at the local offices, who have remained steadfast from the outset, creating constancy of commitment and stability for the network. These leaders have crafted a relationship, built on the use of task forces, and they have encouraged the sharing of jobs and ideas, rather than the fostering of secretive competition.

This powerful partnership, based on mutual respect and support, on clear division of duties, and on hard work, has resulted in creative management, innovative programs, and productive problem solving.

The program needs the strong national direction now in place. In addition, the open relationship that has evolved with the local CIS offices in determining how to accomplish the major tasks is an essential part of running a first-rate service.

As the program expands into larger regional offices, with new staff at both the regional and national levels who have little historical perspective of the network, it will be a challenge to continue this interactive, hands-on, working partnership that has given the CIS one of its greatest strengths.

12) The CIS has provided a valuable service to NCI, helping it to fulfill the institute's priorities as well as its congressional mandate.

The CIS is a major resource for NCI. It represents a high-quality service that is on the cutting edge. It can adapt quickly to national health problems and priorities and can give effective service at the local level to local constituencies.

The CIS is also the key resource at NCI that reaches out to touch people. It was created by the action of Congress, when it passed the National Cancer Act in 1971, which mandated that NCI give patients and physicians access to the latest cancer treatments and included a communica-

tions program to educate the public, patients, and health professionals (24). In its 15 years of operation, the CIS has become a political asset. Its importance has been discussed on the floor of both the Senate and the House of Representatives. Marilyn Tucker Quayle, wife of the former vice president, gave her strong support to the service during the early 1990s (23).

When the CIS has been tied to national priorities, it has proved itself to have the capability to work synergistically with national programs involving other divisions of NCI. The asbestos campaign, targeted at people who had worked in the shipbuilding industry, and Partners in Prevention, which launched NCI's major prevention campaign, are two examples of this effort (8). The clinical trials program added a training program for CIS information specialists to its promotion campaign. It clearly demonstrated that the CIS, trained in proactive counseling, can greatly augment the efforts of the media in reaching a goal of the institute. More callers were told about clinical trials as a result of the proactive counseling than those who asked about it after having seen the clinical trials information in the media. Not only did calls about clinical trials increase, but referrals to trials at NCI-designated cancer centers increased as well (7).

One of the major challenges for the future is to find ways to tie the CIS more directly into major national programs, such as ASSIST, the Centers for Disease Control and Prevention's Breast and Cervical Cancer Mortality Act of 1990, and the "5 A Day for Better Health" education program. These national programs could benefit by using the response mechanism offered by the CIS. Although the CIS is encouraged to coordinate with grantees of national programs at the local level, there needs to be more involvement of the CIS at the national level in early policy determinations as new programs come on-line. Such an effort would ensure the most appropriate use of the CIS in efforts that fulfill NCI and national priorities.

The future of the CIS is bright. Its many accomplishments will help guide it through its next decade, as it is presented with unprecedented opportunities. Five-year contracts are being structured, offering stability to the network and allowing for career building. The role of community outreach and its importance to the network will be strengthened, tested, and resolved. The means of changing the mix of callers will be analyzed and demonstrated. The availability of new technology and computerization of essential elements will challenge the system for a suitable response.

Because it is such a dynamic entity, in many aspects the CIS of the next century may not resemble the CIS of today. In determining the changes that will ensue, it is important that research be given a dominant role. For the CIS to continue its growth and its preeminence in the field—be it in the area of community outreach, of proactive calling, of media use and promotion, or of a dozen other issues—there is a need to structure a program of research that will help to answer the critical questions.

THE PERSONAL FACE OF THE CIS

This monograph has created a picture of the CIS, with descriptions of its essential programs and the statistics that show its effectiveness, as it has grown through its 15-year history. What this monograph has not captured, however, are the feelings of people who have been personally affected by the CIS. In each of the offices, barely a week goes by without a phone call or a letter from someone helped who wishes to say "thank you," to report on experiences and progress, or to ask more questions. Hundreds of letters have been sent spontaneously to CIS offices throughout the country. They give a flavor to the CIS that is worth capturing. (Note: All the names in the following examples have been changed.)

A patient's mother: "Susan learned in a routine exam that she had a mass near her right ovary. Immediate surgery was recommended which Susan understood to mean she would not live to see her 10-year-old son grow up. You helped us identify an oncologist in obstetrics/gynecology at a comprehensive cancer center who could offer a second opinion. . . . That specialist told Susan he believed the mass was benign and why. On May 3, when Susan entered the hospital for surgery, she was able to say to herself, 'I've done everything I can do.' Thankfully, the mass was benign. For Susan and those of us who have shared the terror of these past weeks, gratitude has become a sensitizing recognition of the important role of positive information in health care. All of us, Susan, her family, and her friends appreciate the help you have provided to her."

A male patient: ". . . when I called, I was never at a lower point in my life nor was I ever more alone. Your understanding, your advice, and most of all your taking time to explain all the help available was like a beacon of light in the dark. Thank you again and God bless."

A cancer patient's father: "I have just completed a most informative conversation with Jane, a member of your staff. She went far beyond my greatest expectation in answering questions about my 47-year-old daughter's cancer. Jane represents the rare individual who gives 110% of herself in serving worried patients and worried parents. I congratulate you and thank you for running such a competent operation." The next day brought this in the mail: "I wrote you yesterday, thanking you for the competent caring manner in which Jane responded to my request for information. Now *today* I received the promised literature. FANTASTIC. Were I still in business, instead of this card of thanks, this would be an offer of employment."

A cancer survivor with a recurrence: "As a person devastated by the surprise of finding unexpected secondary cancer and finding myself confronted with a most disheartening unawareness and lack of information on the part of the medical professionals attending my personal health, I must let you know of my deep appreciation of the exceedingly quick, professional, and useful response I received from you. The information you provided me was precisely what I needed to permit me to act on my own behalf as is necessary in the complicated environment of

the quickly changing world of health needs and services. I and my husband are very grateful for your efforts and the system supporting you which was able to put into our hands within 24 hours the most useful and directly applicable information we were able to obtain anywhere."

An undiagnosed patient: "Michelle was not only well informed but extremely courteous and did not attempt to rush with the information she gave me. She listened carefully, answered my questions intelligently, and made me feel that my call was important. I had many questions as this was the first time I had called this number, and at no time did she show any impatience with the amount of information I asked for. I came away from the call feeling I know what I had called to find out and did not feel there were any questions left unanswered to the fullest. Thank you, Michelle, for making me feel comfortable with this call."

A urologist: "A number of my patients have received information by dialing 1-800-4-CANCER. They come to me well informed and are able to ask concise and meaningful questions about their treatment and progress. Without exception, patients have told me that the service they received was immensely helpful and the staff who handled their calls acted in a professional and confidential manner."

A nurse whose mother has cancer: "My mother was diagnosed with cancer yesterday. Blinded and confused, although a nurse, I asked our oncology nurse for more information and a doctor referral. She referred me to your service. I cannot tell you the impact this has made on our family in our decision-making process. Although the road ahead is uncertain and long, you have enlightened us to our disease and to a doctor whom we can turn to for treatment."

One of the favorite patients at the Yale CIS is a man who, more than 11 years ago, called with questions while trying to make a decision on treatment for his prostate cancer. He calls once a year now, following his annual checkup with his doctor, to share his good news of yet another cancer-free year. His call is always an occasion for discussion and joy among the information specialists.

This special monograph has presented a variety of facets of the CIS network: telephone helpline, outreach coordinator, research laboratory, systems innovator. Over the past 15 years, these facets have given the network its character, its distinguishing features. The future will offer the CIS new challenges and new opportunities for evolution and growth. What will remain unchanged is the high-quality, compassionate service, given by individual information specialists, providing help to people when they need it most.

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Proceedings of the
Second National Cancer Institute
Workshop on Taxol and *Taxus*

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PREFACE

This monograph represents a summation of many important advances in Taxol development. Since this Second National Cancer Institute Workshop on Taxol and *Taxus* was held in September 1992, additional milestones warrant recognition.

Semi-synthetic Taxol has been produced from 10-deacetylbaccatin III obtained from a renewable source. Clinical testing of semi-synthetic Taxol will begin early in 1994. Although Taxol from yew bark currently remains the only commercially available drug source, Bristol-Myers Squibb has announced that it plans no further yew bark harvests for Taxol production from public lands and that the Taxol supply is assured.

In September 1993, the Oncology Drugs Advisory Committee recommended to the Food and Drug Administration that Taxol administration by 3-hour infusion be approved for treatment of previously treated ovarian cancer patients.

At the present time, only the 24-hour administration schedule is approved. During their discussion, the Committee noted the need for continuation of clinical trials designed to determine optimal dose and schedule for Taxol administration. They noted that results of palliative treatment in patients with refractory ovarian cancer may not be applicable to other clinical situations, for example, adjuvant therapy of breast cancer.

In December 1993, the Oncology Drugs Advisory Committee recommended to the Food and Drug Administration that Taxol be approved for breast cancer patients whose tumors progressed on or within 6 months of an anthracycline-based adjuvant regimen, or whose cancers progressed after prior anthracycline-containing therapy for metastatic disease.

Susan G. Arbuck, M.D.



Introduction

Samuel Broder, Judith E. Karp*

The development of Taxol¹ is now into its third decade. The process continues to be one of great scientific discovery, exemplifying at each step a bidirectional flow of information between the laboratory and the clinic. The isolation by Wall, Wani, and coworkers in 1971 of this chemically complex product from the bark of *Taxus brevifolia* was followed almost a decade later by Horwitz and Schiff elucidating its unique mechanism of action, namely the ability to stabilize microtubules (which, by definition, are in the polymerized state). In 1989, Taxol was recognized as an important clinical advance, initially for women with platinum-resistant ovarian cancer, by Rowinsky, McGuire, and colleagues. We now know that Taxol has important clinical activity in ovarian, breast, and lung cancers, and preliminary data suggest activity in head and neck cancers and lymphomas. Taxol is not a panacea for cancer, and it is appropriate to temper our enthusiasm with a recognition of the formidable problems that remain. Nevertheless, Taxol does signify progress.

Taxol poses an unprecedented challenge as a natural product of finite natural resources, a product that is chemically complex and difficult to synthesize. Although this may be one of the first times we have been forced to face such issues, it is unlikely to be the last, particularly because the National Cancer Institute (NCI) Cancer Drug Screen continues to focus on natural product derivatives and uncover agents with unique mechanisms of action. We cannot assume an infinite supply as we plan for future drugs and biologics. Taxol is a stellar example of natural product derivatives whose unique mechanisms of action and striking antitumor activity against diverse malignancies were initially identified by the drug screen. In fact, the finding in 1975 of Taxol's prominent activity against B16 melanoma in NCI's earliest drug screening panels prompted the liberation of Taxol from the shelf, where it languished in obscurity as a physicochemically recalcitrant compound, for subsequent clinical development. The challenge of developing Taxol to its fullest clinical dimensions and providing the drug on a continuous basis has demanded and received some of the greatest ingenuity and tenacity that the scientific community can offer. We will return to discuss this issue below.

MOLECULAR PHARMACOLOGY OF TAXOL

Taxol interferes with cell division by manipulating the molecular regulation of the cell cycle. Taxol is a prototype

for agents that directly bind to tubulin and is perhaps unique thus far in that it induces tubulin polymerization, thereby promoting assembly and "freezing" of microtubules in a way that paralyzes the ability of the mitotic spindle apparatus to depolymerize and reorganize itself after the initial stages of mitotic activity. During metaphase, the polymerized spindle serves to organize, condense, and align the chromosomes that have been replicated during S phase, providing checkpoints for orderly chromosomal organization and separation into equal daughter cells at the end of mitosis. Thus, from this point of view, Taxol disrupts physiologic checkpoint functions of a dividing cell.

In addition to constituting the mitotic spindle, microtubules are key components of other cytoskeletal elements that determine cell shape, motility, and membrane functions including transport and signal transduction. By disrupting the dynamic equilibrium between microtubules and their depolymerized tubulin dimers, Taxol also prevents the transition from Go/G₁ through S phase as well as causing lethal metaphase arrest. Moreover, recent studies suggest that Taxol may interact with additional intracellular targets, which, in turn, may converge on the "tubulin pathway" to affect net cytotoxicity. For example, Taxol and lipopolysaccharide appear to activate macrophages by a similar mechanism, namely the tyrosine phosphorylation and consequent activation of microtubule-associated protein (MAP)-2 kinase, an enzyme that triggers changes in microtubule dynamics, thereby promoting the transition from interphase into metaphase. The activated macrophages, in turn, synthesize and express a cascade of cytokines (tumor necrosis factor- α and interleukins-1 β and -6, as examples) that induce a cytotoxic inflammatory and/or immune response.

Taxotere² is a semisynthetic analogue of Taxol, presumably with the same mechanism of action. It is synthesized from 10-deacetylbaccatin III, a biosynthetic precursor of Taxol obtained from the leaves of *Taxus baccata*, the European yew. It is the composition and conformation of the side chain at position C-13 that seem to confer the avidity with which both Taxotere and Taxol bind to tubulin. Taxotere is prepared from a precursor isolated from leaves so that the trees need not be destroyed as they are when bark is collected for Taxol production. Taxotere has been studied in Europe and in the United States at the University of Texas at San Antonio, where responses in patients with ovarian, breast, and lung cancer were detected in phase I trials. NCI has entered into a Cooperative Research and Development Agreement (CRADA) with the pharmaceutical company Rhône-Poulenc-Rorer,

*See "Notes" section at the end of the article.

which will permit NCI to sponsor phase II trials of Taxotere in diverse malignancies, including ovarian, cervical, and lung cancers, and aid in studies necessary to obtain Food and Drug Administration (FDA) approval of a New Drug Application.

For all chemotherapeutic agents, either naturally derived or synthetic, tumor cell resistance is the ultimate limitation to clinical usefulness. The expression of the multidrug-resistance (MDR) gene and its encoded P-glycoprotein (Pgp) membrane pump confers cellular resistance to many of the large, chemically complex natural product derivatives, and it is likely that Taxol and its analogs will be affected by MDR expression as well. To date, *in vitro* and *in vivo* animal model studies suggest that MDR is an important mechanism of cellular resistance to Taxol. Clinically, however, early data indicate that some doxorubicin-refractory patients respond to Taxol. Clearly, there must be additional, nonoverlapping mechanisms of resistance operating for these drugs that have yet to be uncovered. To this end, there are several developmental studies combining Taxol with potential MDR-reversing agents (R-verapamil, quinine, cyclosporin A, and the new nonimmunosuppressive cyclosporin analogue PSC 388, for instance). Such studies should help to define the role of MDR expression in determining eventual clinical outcome in response to Taxol.

The development of a Taxol-resistant murine macrophage cell line that, intriguingly, overexpresses both MDR1 and MDR2 genes and their Pgp isoforms (and also overexpresses tubulin) provides an important opportunity to dissect some of the potential mechanisms by which cells acquire resistance to tubulin-binding agents. Further, an MDR1-positive human myeloma line provides a useful model for study of agents aimed at reversing Pgp-based resistance to Taxol and Taxotere. These models are in place to address the future challenge of biochemical and clinical Taxol resistance.

TAXOL CLINICAL PHARMACOLOGY

As our understanding of the intracellular pharmacology of Taxol continues to increase, so also do we continue to gain important insights into its clinical pharmacology. The central role of the liver and biliary systems in net Taxol disposition has led to an awareness of the importance of the P-450 enzyme family in the overall metabolism of this drug. Certain P-450s metabolize chemotherapeutic agents (for instance, the anthracyclines); other agents can modulate P-450 activity (platinum compounds inhibit various P-450s, for example). The metabolic interaction of Taxol and other drugs has practical therapeutic implications. We will revisit this issue again shortly.

The emergence of hematopoietic growth factors as clinical reagents has changed the way we regard the dose-limiting toxicities of many chemotherapeutic agents. Indeed, the advent of granulocyte colony stimulating factor (G-CSF) and its ability to ameliorate Taxol-related myelosuppression (and, to some degree, oral mucositis) has per-

mitted Taxol dose escalation with greater cumulative Taxol administration. Consequently, Taxol-induced peripheral neuropathy has practically replaced neutropenia as the dose-limiting side effect. Nerve growth factor or other neuroprotective approaches may be important to the total delivery of Taxol and, thus, to the achievement of maximal antitumor effect. We do not yet know, however, that a higher dose of Taxol will necessarily increase its antitumor efficacy, and only well-designed clinical trials can resolve this issue. Nevertheless, the entire area of ancillary biologic response modulation is an important area of research for Taxol and other cytotoxic drugs.

MOLECULAR INTERACTIONS OF TAXOL AND OTHER CYTOTOXIC AGENTS

The combination of Taxol and cytotoxic agents with diverse mechanisms of action is a focus of intensive exploration, both *in vitro* in human tumors and *in vivo* in animal models, including human tumor xenografts. The results in several model systems suggest, but do not prove, that increased antitumor activity can be seen when Taxol is combined with diverse agents, (including cisplatin, VP-16, doxorubicin, and radiation) and support the view that drug scheduling may have great impact on net clinical effect. In the case of Taxol combined with cisplatin, a potentially important therapeutic advance for aggressive ovarian cancers, the optimal sequence is defined by the molecular pharmacology of each drug. Specifically, Taxol has the net effect of downregulating the cell's ability to excise and, thereby, repair the DNA damage induced by cisplatin (in the form of DNA-platinum adducts). In addition, Taxol appears to act as a radiation sensitizer. Perhaps Taxol's induction of cell cycle arrest at the G2/M boundary, where cells are most sensitive to radiation-induced cytotoxicity, is relevant here. The ability to exploit the potential synergy between Taxol and radiation could provide a particularly effective therapy for brain, cervix, lung, and head and neck cancers, where radiation therapy is an integral part of the therapeutic approach.

Taxol Clinical Trials: Optimizing Therapy for a Broadening Spectrum of Cancers

The excitement of preclinical discoveries related to the molecular and clinical pharmacology of Taxol and the expanding cohort of Taxol-related compounds (natural and synthetic) are matched by the results of clinical trials demonstrating that Taxol is an important advance in the therapeutic armamentarium against cancer. The initial promise of Taxol for refractory ovarian cancers has been validated in a total of four phase II studies plus the Treatment Referral Center experience, with response rates of approximately 25% to 30% that could be as high as 50% when Taxol is combined with G-CSF to allow higher and more frequent dosing. However, the issue of a direct relationship between the Taxol dose schedule and clinical outcome needs to be tested in randomized clinical trials.

The activity of Taxol in the poor-risk setting is the foundation for definitive clinical trials to examine the potentially curative role of Taxol in combination with other active agents as first-line therapy for ovarian cancers. The first phase III trial of Taxol, a comparative evaluation by the Gynecologic Oncology Group of Taxol plus cisplatin versus their current standard therapy of cyclophosphamide plus cisplatin as primary therapy for newly diagnosed advanced ovarian cancer, completed accrual in April 1992. Studies to define optimal doses, schedules, modes of delivery, and sequences of Taxol as a single agent and in combination with other therapeutic modalities (including potentially active new drugs such as those of the camptothecin family and radiation therapy) are critical objectives for the ongoing clinical development of Taxol for ovarian (and other) cancers.

Approximately 180 000 new cases of breast cancer occur annually. Roughly 40 000 of these women present with metastatic disease, which is incurable with currently available treatment. The impressive activity of Taxol against advanced breast cancer has now been confirmed in several phase II clinical trials that demonstrate high (50% to 60%) response rates in stage IV breast cancer. Many of these patients, however, had received either no regimen or only one regimen of adjuvant chemotherapy or chemotherapy for metastatic disease. Still, responses were seen even in some of a small group of patients who were previously treated with doxorubicin. These data may imply some degree of non-cross-resistance to drugs commonly used for breast cancer, albeit in small numbers of patients thus far, and suggest that we have much to learn about the clinically important mechanisms of Taxol resistance. In this regard, a multi-institutional trial of special importance is designed to determine the full spectrum of Taxol activity and/or cross-resistance in true doxorubicin-refractory breast cancer. A similar study is planned for vinblastine-refractory patients. Early studies combining Taxol with doxorubicin and/or G-CSF are yielding high objective response rates (more than 60% with about 10% of those being complete remissions) in women with stage IV breast cancer, either as first-line therapy or for recrudescence following adjuvant therapy (chemotherapy including doxorubicin or hormonal therapy). Thus, for breast cancer as for ovarian cancer, Taxol holds promise as a potentially non-cross-resistant therapeutic agent. Likewise, clinical trials to realize Taxol's full potential and optimal role in breast cancer, including adjuvant therapy, are a surprisingly high priority.

The activity of Taxol as a single agent in non-small-cell lung cancers (and, perhaps preliminarily, in extensive small-cell lung cancers) sets the stage for multiarm comparative trials of Taxol at two different doses, with and without cisplatin and G-CSF. Encouraging responses are also being seen in head and neck cancers, where similar trials to examine the efficacy of Taxol in combination with cisplatin, G-CSF and/or radiation are under development. The role of Taxol in refractory lymphomas is being explored in a correlative laboratory-clinical trial designed to address the clinical pharmacology and differential toxicities

of prolonged continuous infusion Taxol, the relationship between MDR1 expression and clinical response, and the presence and magnitude of any Taxol-induced changes in tubulin during continuous infusion therapy.

It is worth emphasizing that there is a great deal that we still do not know. It has not been formally proven that Taxol in combination with other agents is superior to Taxol as a single agent. It is not known whether increasing the dose intensity of Taxol will confer clinical advantages in common cancers. And finally, we still do not know for sure whether Taxol can bring about greater cure rates in the true sense of that term.

Providing Adequate Drug to Ensure the Future of Taxol Research and Application

The development of alternative sources of Taxol, for the dual purpose of ensuring sufficient drug supply and reasonable cost when the drug is approved and marketed, continues to be a critically high priority. Staff within NCI's Developmental Therapeutics Program have solved monumental logistical problems. NCI, through the Department of Health and Human Services, has entered into a Memorandum of Understanding with the Department of Agriculture and the Department of the Interior to facilitate efforts to obtain an adequate supply of Pacific yew tree bark on federal lands. Although previously Taxol could be obtained only from the bark, now Taxol also can be obtained from renewable parts of the Pacific yew tree (e.g., twigs, needles) and from cultivated and wild yew species growing worldwide. At present, Taxol for clinical use still comes from the bark of the Pacific yew, but this source will gradually be phased out as renewable sources become available. Production of Taxol has also been observed in plant tissue culture, raising the hope that batch culture processes might be developed for Taxol production. Recent progress in Taxol synthesis holds promise for eventually providing a continuous source of Taxol for clinical use. The ability to develop a high-yield, commercially viable total synthesis of Taxol from cheap starting materials may no longer be out of reach. The supply of Taxol has increased substantially over the past year following the establishment of a CRADA between Bristol-Myers Squibb and NCI. As a result, progress can be reported in multiple areas. The development of alternative sources of Taxol, Taxol derivatives, and novel chemical approaches to Taxol synthesis or semisynthesis and the interactions fostered with the pharmaceutical industry and multiple governmental agencies to provide adequate amounts of drug serve as templates for development of other complex natural products.

Another administrative innovation spurred by Taxol is the creation of the NCI Treatment Referral Center, based at NCI-supported cancer centers, to provide information regarding standard treatment options, clinical trials, patient eligibility, and listings of investigational drugs for optimal patient management. The Treatment Referral Center also coordinates clinical trials that accrue patients at the participating cancer centers. In September 1991,

based on data indicating that Taxol was effective in women who no longer responded to standard therapy, in collaboration with Bristol-Myers Squibb, NCI made Taxol available to women with refractory ovarian cancer who have received three prior chemotherapy regimens (two prior regimens as of July 1992). Treatment is provided through the Treatment Referral Center at one of 39 NCI-designated cancer centers. By July 1992, more than 1700 patients with heavily treated ovarian cancer had received Taxol through this mechanism. The response rate in the first 500 patients who are evaluable for response is 24%.

THE NEXT CHAPTER

In 1990, there was only enough Taxol to treat 500 women. Today, more than 4600 women with ovarian and breast cancers have received Taxol in NCI-sponsored clinical trials, and upcoming clinical trials are projected to accrue more than 1500 women with ovarian cancer, 1200 women with breast cancer, and additional women with cervical and uterine cancers. An advisory committee has recommended that the FDA approve Taxol for women with refractory ovarian cancer. Phase II evaluations of Taxol are now underway in a wide variety of malignancies—for example, bladder, brain, esophageal, liver, pancreatic, and testicular cancers and mesotheliomas and multiple myeloma. The ability to carry out such developmental studies and to define the breadth of Taxol's clinical activities, both for clinical trials and for compassionate treatment programs through the Treatment Referral Center, is the direct result of the continuous efforts to provide an adequate and renewable source of the drug. Currently, NCI is sponsoring 48 Taxol studies, with another 23 protocols in review and approximately 10 concept proposals under development. The Treatment Referral Center program has now expanded to include women with refractory

breast cancer. Upon approval of Taxol by the FDA, it is likely that many of the activities of the Treatment Referral Center will no longer be necessary.

The obstacles to uncovering Taxol's full therapeutic potential have required the establishment of novel mechanisms, both scientific and administrative, that are paradigms for the preclinical and clinical development of other natural products. The successful development of Taxol is directly attributable to the combination of vision and perseverance of many members of NCI's Division of Cancer Treatment—Bruce Chabner, Matt Suffness, Michael Grever, Gordon Cragg, Ken Snader, Saul Schepartz, Susan Arbuck, and Michael Friedman, to name just a few. And because of these creative, effective, and unending efforts, as the Second NCI Workshop on Taxol and *Taxus* clearly demonstrates, we have just barely begun to tap into the full possibilities of Taxol against a broadening spectrum of cancers. The reward for these groundbreaking efforts is the current availability of sufficient quantities of the drug for patients with responsive malignancies and continuing realization of Taxol's promise to change the outlook for some of these devastating diseases. But there is still much hard work ahead.

NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

²Taxotere is used in this monograph to refer to the drug that now has the generic name docetaxel and the registered trade name Taxotere® (Rhône-Poulenc-Rorer Pharmaceuticals Inc., Collegeville, Pa).

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Summary—Session I: Supply—Harvest of *Taxus brevifolia*

Saul A. Schepartz, Session Chairman*

The supply of Taxol¹ from the bark of *Taxus brevifolia* was the primary concern of session I, although some discussion of alternative sources, which was the main subject of session II, was included. The session opened with an overview by Dianne DeFuria of Bristol-Myers Squibb (BMS) of the status of Taxol production and availability. The terms of the Cooperative Research Development Agreement (CRADA), awarded competitively to BMS and signed in January 1991, assign to BMS the responsibility for providing the drug to the National Cancer Institute (NCI) for its continuing clinical trials and for developing alternative sources as soon as possible. With the help of agreements established with the U.S. Department of Agriculture's Forest Service and the U.S. Department of the Interior's Bureau of Land Management, and by working through its contractor Hauser Chemical Research, BMS was able to obtain over 850 000 lbs of bark from federal lands and about an equal amount from private property in 1991. As a result, BMS is now able to provide 50 000 vials of finished product monthly to NCI. At the time of the workshop, BMS expected to collect about an equal amount in 1992 and by 1993, expected to start obtaining some material from an alternative source, through semisynthesis from precursors obtained from the needles of *Taxus baccata* collected in Europe and Asia. Projections suggested that the need for bark will be eliminated completely by 1996, utilizing a variety of alternative sources being developed in collaboration with many of the groups speaking at this meeting.

The collection and processing of bark was discussed in more detail by Dean Stull of Hauser Chemical Research. Major improvements in both scale-up capacity and the purification process have occurred. Although their initial facility could process up to 24 kg yearly, their 1991 capacity was 130 kg, with a further increase to 230 kg projected for 1993. With regard to chemical purification, their yield had increased from 1 kg per 35 000 lbs of bark to 1 kg per 16 000 lbs, in spite of the difficult problems in purifying Taxol, such as its separation from cephalomannine. Active efforts were also underway to develop new processes for the conversion to Taxol of other taxanes present in the biomass, which could increase the overall yield by a factor of 2 or 3.

The critical role of the Forest Service and the Bureau of Land Management in making Pacific yew available for harvest was discussed by Richard Miller of the Forest Service. Prior to 1991, a total of about 200 000 lbs of bark had been provided to NCI. Based on agreements among

all of the federal agencies and with BMS, the Forest Service and Bureau of Land Management were successful in providing in excess of the requested amounts (750 000 lbs) in both 1991 and 1992 without impinging on protected areas. Guidelines have evolved for the management of yew harvest to assure that bark is not wasted, that the species is protected, and that the entire process is carried out in accordance with provisions of the Endangered Species Act and other legislation.

Problems related to genetic variation in *T. brevifolia* were covered by Nicholas Wheeler of the Weyerhaeuser Company. The company began to investigate the cultivation of the Pacific yew in 1987. In 1988, Weyerhaeuser initiated a study of the genetics of the species to determine the degree of variation of relevant traits. They discovered that about 10% of the allozyme variation was among populations, a much higher degree of such variation than in pine, for example. The primary variation, however, is within populations, representing about 89% of the allozyme variation. Variation among regions is very small. Based on taxane analyses in conjunction with these genetic studies, Wheeler suggested that for utilization of leaves, baccatins should be targeted. In selecting sources of material, the region should be ignored. Instead, emphasis should be placed on individual trees, families, and populations. In addition, he noted that environment plays a significant role in trait expression.

Exploring further the factors affecting taxane content in *T. brevifolia*, Nan Vance of the Forest Service's Pacific Northwest Research Station presented data from research conducted with Rick G. Kelsey, also of the Pacific Northwest Research Station, on the content of Taxol, baccatin III, and cephalomannine in both bark and needles collected under a variety of conditions, such as variations in light, season, and genetics. Sampling 20 trees, 10 growing in the shade of the forest canopy and 10 in the opening of a 6-year-old clearcut, Kelsey and Vance found great variations in content of the individual taxanes under different conditions. For example, there was a fourfold higher level of Taxol in bark than in needles, and shaded trees had more Taxol in bark than those in the open area. On the other hand, cephalomannine in needles showed an opposite effect. Baccatin III was generally higher in needles than in bark, and higher than Taxol in needles. There is, overall, considerable variation in content among individual trees and within trees depending on when they were sampled. Furthermore, these variations are different for the individual taxanes. The optimization of growing and harvesting conditions is, thus, exceedingly complex and

*See "Notes" section at the end of the article.

will vary depending on the tissue and specific compound desired.

Sally Campbell of the Forest Service's Pacific Northwest Region, who heads the interagency group developing an Environmental Impact Statement (EIS), provided a progress report on the efforts of that group. The EIS, which is a necessary component of the eventual drug approval by the Food and Drug Administration, involves three collaborating agencies: Forest Service, Bureau of Land Management, and the Food and Drug Administration. The EIS will discuss the effects of harvesting all parts of the tree, including needles, wood, and bark, even though only bark is used at this time. A number of alternatives will be presented, alternatives that will vary in terms of areas available for harvest, the amount of yew that can be removed from any local area, and consistency with "An Interim Guide to the Conservation and Management of Pacific Yew," a document that is serving as the basis for current management practices. At the time of the workshop, a draft EIS was expected to be published late in 1992 and the final version in the spring of 1993.

Finally, Bruce Manheim of the Environmental Defense

Fund presented that organization's viewpoint on the management of the yew harvest, which they believe has resulted in unnecessary loss of biomass. He was particularly concerned with the need for practicing "pre-logging" harvest of the yew, a practice that was implemented on much of the federal land in 1992. He applauded the enactment by Congress this year of the Pacific Yew Act, which calls for management practices that minimize waste, requires harvesting before logging operations, and requires practices that allow for regeneration of the tree.

NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Summary—Session II: Alternative Sources of Taxol

Gordon M. Cragg, Session Chairman*

The projected elimination of the bark of *Taxus brevifolia* as a source of bulk supplies of Taxol¹ by 1996 reflects the substantial progress that has been made in the development of alternative sources since the first Taxol workshop in June 1990. Bristol-Myers Squibb (BMS) Company and the National Cancer Institute (NCI) have devoted considerable resources to identifying and developing viable alternative sources, through both in-house research and collaborative programs with other organizations.

In the medium term, there is no doubt that the major source of Taxol and related taxanes will be the leaves, harvested from both wild and cultivated *Taxus* species. The pioneering studies in this area were performed by French workers who isolated the key Taxol precursor, 10-deacetylbaccatin III, in yields of up to 0.1% from the leaves of cultivated *Taxus baccata*, and developed methods for its conversion to Taxol and Taxotere². Dr. Guéritte-Voegelein of Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, Gif-sur-Yvette, presented details of these studies and a comparison of these compounds as inhibitors of microtubule disassembly; Taxotere was found to be the most potent compound in this respect.

The large-scale isolation of Taxol, baccatin III, and 10-deacetylbaccatin III is associated with a number of problems which were discussed by several speakers. The content of these and other taxanes in needles varies considerably from one *Taxus* species to another and even within the same species, depending on the geographical location of collection, environmental conditions, and time of harvest.

Dr. James McChesney reported on the study of ornamental yews being conducted by the Research Institute of Pharmaceutical Sciences at the University of Mississippi, in collaboration with Zelenka Nursery, Inc., and the Ohio Agricultural Research and Development Center. Samples of 40 ornamental cultivars have been analyzed, and Taxol contents were found to vary from 0.005% to 0.07%. On the basis of these analyses, the cultivar, *Taxus x media* "Hicksii" was identified as a potential, renewable source of Taxol, and 100 000 lbs of clippings were mechanically harvested, dried, and submitted to NCI and BMS for extraction and processing. This large-scale harvest was supported through an interagency agreement between the U.S. Department of Agriculture and NCI.

The most critical factor affecting the use of needles as a source of Taxol and key taxanes is the drying process; lack

of proper control in this process can lead to drastic reduction in Taxol content. Current experience indicates that the Taxol content is best maintained by drying the needles still attached to the stems at temperatures in the range of 40–50 °C. Detaching the needles from the stems prior to drying leads to significant reduction in Taxol content. Dr. Robert Hansen of the Ohio Agricultural Research and Development Center reported on an exploratory study using commercial grain-bin drying systems for drying large quantities of *T. x media* "Hicksii." Results suggested that such systems are not effective in meeting the currently accepted tolerances for drying *Taxus* biomass and may require extensive modification. Studies are in progress to determine the parameters necessary for optimal drying.

The importance of the drying process was also emphasized by Dr. Ezio Bombardelli of Indena SpA, Milan, who discussed the industrial-scale production of baccatin III and 10-deacetylbaccatin III from the needles of *T. baccata*, *Taxus wallichiana*, and other *Taxus* species. Large-scale collections of needles from such wild sources are inevitably associated with delays between the harvesting, drying, and extraction steps, delays that can result in substantial decreases in yields. Great caution also has to be exercised in the isolation and purification of these compounds due to their sensitivity to conditions of pH, chromatographic adsorbents, such as silica and alumina, and the length and temperature of processes involving concentration of extracts and fractions. Common degradations that can occur are partial hydrolyses, epimerizations, and oxidation. Another complicating factor is the presence of many other taxanes which can interfere with the purification process; more than 10 compounds containing cleaved oxetane rings, as well as several oxygenated derivatives of the baccatins, have been isolated. Despite these problems, Indena has developed a good process for large-scale isolation of the baccatins and will be providing bulk supplies to BMS for semisynthetic conversion into Taxol.

The key to the effective production of Taxol from the renewable *Taxus* needle resources is the efficient attachment of the side chain to the baccatin III precursor. Since the first report of the conversion of 10-deacetylbaccatin III to Taxol by French workers in 1988, improved procedures have been developed. Dr. Robert Holton discussed several efficient esterification methods developed by his research group at Florida State University. The processes, which involve the reaction of suitably substituted β -lactams or oxazinones with a protected baccatin III derivative, give overall yields of Taxol ranging from 85% to

*See "Notes" section at the end of the article.

98% and can be readily adapted to the synthesis of a wide variety of Taxol congeners having modified C-13 side chains. The technology has been licensed to BMS and, at the time of the workshop, the bulk production of Taxol by this method was anticipated in 1993.

Although the renewable *Taxus* needle resources, together with semisynthesis from baccatin III, are expected to be the major source of Taxol for the foreseeable future, it is anticipated that tissue cultures of *T. brevifolia* and other related species will make significant contributions to bulk production in the long term. Dr. Michael Shuler of Cornell University discussed the studies being performed in collaboration with the U.S. Department of Agriculture, Phyton Catalytic, Hauser Chemical Research, and Colorado State University to determine the effects of various treatments in suspension cultures on dependent parameters, such as growth rate, Taxol production rate, ratio of extracellular/intracellular Taxol, and the formation of other taxanes. A wide range of responses to different plant growth regulators and vitamin treatments was found in culture, even among different cell lines of the same species (*T. brevifolia*). A study of the kinetics for a cell suspension culture of a high producer of Taxol, derived from *T. baccata*, over a 26-day culture period, indicated a fourfold increase in fresh cell weight after a lag phase of 4 days. The growth curve was slightly biphasic in character, and Taxol was first seen at 13 days and increased sharply after 20 days. Taxol was found only in the medium, and a level of 3.9 mg/L was achieved after 26 days. Taxol was dominant over other taxanes found in the medium.

Substantial progress is being made in approaches to the total synthesis of Taxol, as illustrated by the studies reported by Dr. Paul Wender of Stanford University. Dr. Wender's approach uses, as its starting material, pinene, a constituent of pine trees and a major component of industrial solvents such as turpentine. Pinene, which possesses

the same handedness as Taxol, is converted to the tricyclic core of Taxol in only five synthetic steps; an additional three steps introduce the complete functionality and stereochemistry of the Taxol A ring, to provide a tricyclic derivative having all the functionality required to introduce the remaining groups attached to the B and C rings of Taxol. The eight-step sequence is sufficiently straightforward to be adapted to a large-scale production. Work is now proceeding on the final phase requiring elaboration of the remaining C ring appendages. Pinene has been shown to represent a superb and inexpensive starting material for the practical synthesis of Taxol and Taxol analogues, and this research provides an excellent example of the application of basic research to practical needs.

Although total synthesis is unlikely to make a major contribution to the bulk supply of Taxol in the near future, the synthetic approach provides a means for systematically determining the structural requirements for Taxol's anticancer activity, and may be used in the design and development of simpler analogues which could prove to be more effective and less costly than Taxol itself.

NOTES

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²Taxotere is used in this monograph to refer to the drug that now has the generic name docetaxel and the registered trade name Taxotere® (Rhône-Poulenc-Rorer Pharmaceuticals Inc., Collegeville, Pa.).

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Summary—Session III: Methods and Reagents

Kenneth Snader, Session Chairman

Two years ago, at the time of the last workshop, the tasks of locating alternative supplies of Taxol¹ and optimizing the recovery of Taxol from natural sources were clearly identified, but the tools for better detection and isolation had not been developed. During the intervening 2 years, numerous groups focused on the difficulties and, as a result, substantial progress has been made. In a direct approach, Hauser Chemical Research, Inc., the principal producer of bulk, human-use Taxol, announced that it had improved the process for the recovery of Taxol from Pacific yew bark. They reduced the amount of bark necessary to produce 1.0 kg of Taxol from 35 000 lbs to less than 15 000 lbs. This is certainly an important improvement, but even more important is the effort to find new methods and sources of Taxol that do not require the harvesting and destruction of the wild Pacific yew, *Taxus brevifolia*. To accomplish this, new, sensitive methods for detecting Taxol and other taxanes in a variety of natural sources, as well as improvements on the purification procedures that would reduce the costly and complicated chromatographic processes necessary to prepare Taxol from its crude biological source, were needed. Session III highlighted several new procedures for both isolating and detecting Taxol and taxanes in biological materials, as well as defining the level of understanding of the biosynthetic pathway for production of Taxol.

Several reports have emerged to demonstrate that Taxol is present in the needles of various *Taxus* species, but they also point out that the mixture is considerably more complex, that there are numerous other isomers, and that the product is metabolically more labile and requires special handling. A sophisticated new technique that has been applied most successfully to the food industry, is the use of supercritical fluid extraction. T. Castor of Bio-Eng, Inc., described the successful application of this technique to both bark and needles from *T. brevifolia* in which he obtained a 99+ % recovery of Taxol. He also described the advantages of the procedure in which he was able to separate an impurity present in the needles that coelutes chromatographically with Taxol. Designs and apparatus are available to allow scale-up of the process to a production level of up to 200 kg/year.

In the search for other sources of Taxol, several observations have been reported to indicate that the Taxol content of various *Taxus* plants varies with the type of tissue and its location on the plant. The development of a competitive inhibition enzyme immunoassay reported by P. Grothaus of Hawaii Biotechnology Group, Inc., which

uses three monoclonal antibodies developed against Taxol, baccatin III, and generic taxanes, respectively, permits the detection of these products down to the 10^{-3} micromolar range and permits analysis of tissue samples as small as single needles. Even more encouraging, from a preparative standpoint, is some preliminary success with a Taxol-specific immunosorbent containing immobilized monoclonal antibody that will bind Taxol from an aqueous methanol solution and then release it on elution with a methanol gradient.

Perhaps the most sensitive method for identifying Taxol and other taxanes in natural plant tissue uses tandem mass spectroscopy. This method gives more physical evidence of the chemical nature of the taxane than can be obtained from thin-layer chromatography or high-pressure liquid chromatography methods and is sensitive into the picogram range. C-j. Chang of Purdue University presented his most recent results of a technique in which he combined MS/MS tandem mass spectroscopy with desorption chemical ionization to measure the Taxol content from a single needle of *Taxus cuspidata*. The detection limit is less than 500 pg, and the method can identify not only Taxol but also cephalomannine and baccatin III, all from the same sample in a total of less than 1 hour for both extraction and analysis.

Detecting a compound with a very sensitive assay and following it through any metabolic modification is most commonly done using a radiolabeled compound. Specific placement of the label is necessary so that equilibration reactions in a physiological milieu will not remove or scramble the label. Also, because the structure of Taxol can be viewed as a core-bridged ring taxane nucleus with a functionalized β -amino acid ester, it is important to determine where metabolic reactions occur and whether the parent molecule or some modified structure is important for its biological effect. J. A. Kepler of Research Triangle Institute described an elegant synthesis of 3'-tritiated Taxol where the radiolabel is incorporated into the side chain of Taxol, using a modification of Holton's coupling reaction with the appropriately tritiated β -lactam. Also, by using manganese dioxide oxidation of baccatin III, he was able to prepare the 13-keto product which, after suitable protection, was reduced with tritiated borane to give an intermediate that was readily converted into 13-tritio Taxol. Thus were made available the appropriate tools to evaluate the metabolic fate of intact Taxol as well as to examine the possibility of an equilibration of the side chain of the molecule, either in mammalian metabolism or possibly through natural plant metabolism.

Finally, new results in studying the biosynthesis of

*See "Notes" section at the end of the article.

Taxol hold important potential in light of the recent promising results in plant tissue culture as a possible source of future Taxol (taxane) production. Like antibiotic fermentation processes, production of secondary metabolites can often be enhanced if suitable precursors are provided to the producing organism. Knowledge of the biosynthetic pathway for production of Taxol provides important insight into the nature and importance of various intermediates. N. Lewis of Washington State University described his progress in elaborating the sequence and enzymatic components of Taxol biosynthesis. Using cell-free enzyme isolates from *T. brevifolia* and appropriately radiolabeled precursors, he has been able to focus on the first of five important transitions in the pathway, the cyclization of geranylgeranyl pyrophosphate to a taxadiene precursor. From a partially purified and characterized enzyme prep-

aration, he has isolated a diterpene olefin cyclase. The low level of cyclase activity may be due to its role as the rate limiting step in taxane biosynthesis. Nevertheless, the preliminary results are encouraging.

NOTES

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Clinical Development of Taxol

Susan G. Arbuck, Michaele C. Christian, Jason S. Fisherman, Lorraine A. Cazenave, Gisele Sarosy, Matthew Suffness, Jonathan Adams, Renzo Canetta, Katharine E. Cole, Michael A. Friedman*

Taxol is the first of a novel class of anticancer drugs, the taxanes. Taxol's unique effects include its ability to polymerize tubulin into stable microtubules in the absence of cofactors and to induce the formation of stable microtubule bundles. During its development, formidable challenges were overcome: a suitable formulation was developed, an adequate supply was ensured, severe hypersensitivity reactions were diminished in incidence and severity, and clinical efficacy was demonstrated. Phase II evaluation is still underway; to date, clinical efficacy has been demonstrated in ovarian, breast, non-small-cell lung, and head and neck cancer. Response rates were low in early studies in melanoma, prostate, colon, cervix, and renal cancer, but for these tumors, additional evaluation is ongoing with a higher Taxol dose or different schedule. In December 1992, Food and Drug Administration approval was granted for use of Taxol as second-line therapy in ovarian cancer patients. Nevertheless, important questions regarding optimal use of this important new drug remain. These include determination of optimal dose and schedule and development of suitable combination chemotherapy regimens. The clinical development of Taxol and current status of phase I, II, and III clinical trials are reviewed. [Monogr Natl Cancer Inst 15:11-24, 1993]

DISCOVERY, STRUCTURE, AND PRECLINICAL ACTIVITY

Thirty years ago, samples of *Taxus brevifolia*, the Pacific yew tree, were collected from the old-growth forests of the Pacific northwest, as part of a National Cancer Institute (NCI) program to screen natural products for anticancer activity. Preliminary screening indicated that an extract from the tree had activity against the KB cell line and mouse leukemia cells (1). Later, in vivo activity was demonstrated in the Walker 256 carcinosarcoma, P1534 and L1210 leukemia models, and in B16 melanoma and MX-1 human breast cancer xenograft models (2).

Taxol¹, the active component of the extract, was isolated in pure form in 1969, and its structure was described by Wani et al. in 1971 (Fig. 1) (1). Taxol is a complex diterpene. It has a taxane ring system with a four-membered oxetane ring and an ester side chain at position C-13. This C-13 side chain is necessary for cytotoxic activity in mammalian cells (3). Taxol has since

been found in the bark, leaves, stems, and roots of a variety of *Taxus* species (4).

In 1977, Taxol was accepted for clinical development by the NCI Division of Cancer Treatment's Decision Network. Despite its novel structure and effectiveness in murine models, there was only modest early enthusiasm for clinical trials. Taxol had broad, but not impressive, activity in preclinical model systems (2,5). Preliminary studies of its mechanism of action indicated that the drug was a mitotic inhibitor, superficially similar to the vinca alkaloids (6). Maytansine, a potent mitotic inhibitor, had failed clinical testing in the late 1970s, further dampening enthusiasm for this area of anticancer drug development. Therefore, the new compound, which was in scarce supply and poorly soluble, initially was not given a high priority (5).

Table 1 summarizes the 30-year history of Taxol development.

MECHANISM OF ACTION

Interest in Taxol increased in 1979 when Schiff et al., described its unique mechanism of cytotoxicity (7,13). In contrast to other antimitotic agents, such as vinca alkaloids and colchicine, which inhibit the polymerization of tubulin, Taxol promoted the assembly of tubulin and stabilized the resulting microtubules.

Microtubules are important structural elements in eukaryotic cells. In addition to forming the mitotic spindle and channels for neurotransmitter secretion, they regulate cell shape, anchor surface receptors in the plasma membrane, and affect motility of cilia. Microtubules normally form through the polymerization of α - and β -tubulin subunits with a requirement for guanosine 5'-triphosphate (GTP) and various microtubule-associated proteins (MAPs). In the presence of Taxol, polymerization occurs even in the absence of GTP or MAPs, and even at low temperatures which normally inhibit in vitro polymerization (14,15). In addition, Taxol-treated microtubules resist disassembly under conditions (4 °C or 4 mM CaCl₂) that usually cause dissolution of the polymer (7,16,17). Thus, the normal equilibrium of assembly and disassembly is shifted toward microtubule formation. Disruption of this equilibrium interferes with cell division and normal cellular activities involving microtubules.

Taxol binds preferentially to polymerized microtubules, rather than to the α - β tubulin dimer, with a K_D of approximately 1 μ M (16). The specific binding site for Taxol is on

*See "Notes" section following "References."

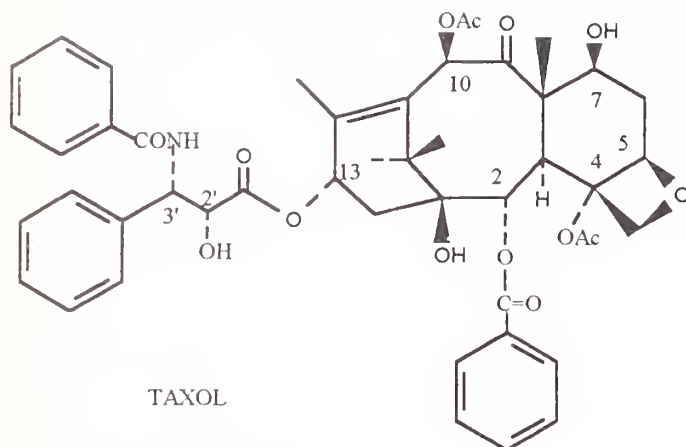


Fig. 1. The structure of Taxol.

the microtubule, unlike that for colchicine or the vinca alkaloids, which is on unpolymerized tubulin (18). Taxol is a potent inhibitor of eukaryotic cell replication and blocks cells in late G₂-mitotic phase of the cell cycle (13). Mitotic arrest has been observed in normal esophagus, stomach, small intestine, colon, liver, skin, bone marrow, and testis specimens obtained at autopsy from a patient who received Taxol 11 days before death (19).

Cells treated with clinically achievable concentrations of Taxol initiate mitosis with disappearance of the nuclear membrane and condensation of chromosomes, but they lack a normal mitotic spindle. Instead they form multiple abnormal asters or arrays of microtubules distributed throughout the cytoplasm (20,21).

Taxol triggers tumor necrosis factor and interleukin-1 production in macrophages. Effects of these molecules may contribute to antitumor activity (22,23) [discussed elsewhere in this monograph by Carboni et al. (24)]. Some molecules associated with oncogenesis appear to interact with tubulin and/or microtubules. For example, the *mos* oncogene appears to bind to and stabilize microtubules (25). The product of the tumor-suppressor gene, p53, and the T-antigen of SV-40, both bind to tubulin in a ternary complex (26). In addition, the CDC-2-kinase, which helps initiate mitosis in eukaryotic cells, phosphorylates tubulin (27). Our understanding of the mechanism(s) of action of Taxol and the consequences of altering microtubule dynamics is incomplete, but clearly, tubulin represents a critical potential target for control of cell division and growth regulation (5).

PHASE I CLINICAL TRIALS

Phase I clinical trials with Taxol, which are summarized in Table 2, began in 1983 (28-39). The first high-pressure liquid chromatography method for measuring Taxol in body fluids was developed at Albert Einstein Cancer Center (37). The human pharmacology of Taxol is presented in detail elsewhere in this monograph by Rowinsky (40). Taxol plasma concentrations of approximately 1 μ M were achievable in humans with the 24-hour schedule of Taxol administration (2). Notably, lower concentrations resulted in microtubule perturbations and cytotoxicity in vitro. Higher concentrations have been achieved with the shorter administration schedules. Mean values for steady-state

Table 1. Thirty-year history of Taxol development

Year	Event	Reference
1963	<i>T. brevifolia</i> samples collected for screening.	(2)
1964	Activity in KB cytotoxicity assay.	(1)
1966	In vivo activity in Walker 256, P1534, L1210 leukemia.	(2)
1971	Isolation and structure reported.	(1)
1974	Activity in B16 melanoma.	
1977	Accepted for preclinical development.	
1978	Recognized as mitotic spindle poison.	(6)
1979	Unique mechanism of action as microtubule stabilizer.	(7)
1980	Formulation completed. Bulk supply adequate. Accepted preclinical toxicology.	
1983	Phase I clinical trials began.	
1985	Phase II clinical trials began.	
1989	Activity reported in platinum-refractory ovarian cancer.	(8)
1990	First NCI workshop on Taxol and <i>Taxus</i> .	
1990	First phase III trial began in suboptimally debulked cancer.	
1991	Cooperative Research and Development Agreement: National Cancer Institute and Bristol-Myers Squibb (January).	
	NCI Treatment Referral Center (TRC 9103) Protocol for refractory ovarian cancer began (September).	
	Activity reported in breast cancer.	(9)
1992	Activity reported in lung cancer and head and neck cancer.	(10-12)
	New drug application submitted to FDA by Bristol-Myers Squibb (July).	
	NCI Treatment Referral Center protocol for refractory breast cancer began (October).	
	Three phase III trials initiated in ovarian cancer.	
	Taxol NDA approved (December).	

Table 2. Phase I trials of single-agent Taxol

Institution	Schedule*	Recommended phase II dose (mg/m ²)	Dose-limiting toxicity	Premedications	Reference
M. D. Anderson	1 h daily × 5	150 (30 × 5)	Leukopenia	No	(32)
Wisconsin	6 h daily × 5	150 (30 × 5)	Leukopenia	No/Yes	(30)
Dana-Farber	24 h daily × 5 (120 h)	150 (30 × 5)	Leukopenia, mucositis	No/Yes	(38)
Memorial	3 h	†	Hypersensitivity	No	(31)
Hopkins	6 h	Minimal prior treatment: 212 Extensive prior treatment: 170	Leukopenia	No/Yes	(29)
Einstein	6 h	250	Neuropathy, leukopenia	No	(37)
San Antonio	6 h	225	Leukopenia, neuropathy	Yes	(38)
Einstein	24 h CIV [‡]	250	Neuropathy, leukopenia	Yes	(36)
Hopkins (acute leukemia)	24 h CIV every 14-21 d	315 mg/m ²	Mucositis	Yes	(34)
With G-CSF					
NCI Medicine Branch	24 h	250	Neuropathy	Yes	(35)
Intraperitoneal					
GOG [§]	Every 3 wk	≤125 (Not recommended. Weekly trial in progress)	Abdominal pain	Yes	(39)

*Treatment was planned every 3 wk unless noted.

†Not recommended as administered in this trial without premedication.

‡Continuous IV infusion.

§Gynecologic Oncology Group.

volumes of distribution are large (55–183 L/m²) suggesting avid binding to circulating or cellular proteins, possibly tubulin. Despite extensive binding to plasma proteins (95% to 98%), Taxol is readily eliminated from plasma (33,36,37). The beta half-life of Taxol is 4 to 6 hours.

Renal clearance has accounted for an insignificant proportion (approximately 5%) of total systemic clearance. The principal mechanisms of systemic clearance have not been defined precisely, suggesting that metabolism, biliary excretion, or extensive tissue binding are responsible for the bulk of systemic clearance. High Taxol concentrations and hydroxylated metabolites have been found in both rat and human bile (41,42). These studies are discussed in greater detail in this monograph by Monsarrat et al. (43). Studies with radiolabeled Taxol are planned to explore further Taxol disposition in patients.

Major Toxicities

Hypersensitivity reactions. Because of its limited aqueous solubility, Taxol is formulated in Cremophor EL[®] and ethanol. Cremophor EL has been associated with bronchospasm, hypotension, and other manifestations of hypersensitivity, particularly following rapid administration (2). Although Cremophor EL is used to formulate other drugs including teniposide, vitamin K, and miconazole, the Taxol formulation requires the highest Cremophor EL concentration per dose (2).

Noteworthy hypersensitivity reactions were reported in as many as 18% of patients in early phase I trials. Allergic manifestations varied in severity and included anaphylaxis, dyspnea, hypotension, flushing, urticaria, rash, and pruritus (44). The frequency of severe reactions and the occurrence of one death almost terminated clinical devel-

opment. However, the persistence of the investigators from Albert Einstein and Johns Hopkins Cancer Centers, despite tremendous difficulties and some controversy, resulted in successful completion of phase I trials and, thus, permitted Taxol development to continue. Because the hypersensitivity manifestations were similar to those due to iodinated radiologic contrast dyes, the premedication regimen used to prevent contrast-dye hypersensitivity reactions was successfully adopted by these investigators, with concurrence of NCI, for routine use with Taxol, in early 1985.

A review of the early trials suggested that the incidence of hypersensitivity reactions was lower with 24-hour than with 1- or 3-hour administration schedules. Because objective responses were also seen with the 24-hour schedule, it was chosen for phase II evaluation. When the 24-hour schedule was used and when oral or intravenous dexamethasone (6 and 12 hours pretreatment), diphenhydramine, and an intravenous H₂ blocker, usually cimetidine (30 minutes pretreatment), were routinely administered, the incidence of serious anaphylactic reactions decreased to 3% or less (unpublished data on file, NCI and Bristol-Myers Squibb).

Although Cremophor EL may be responsible for the hypersensitivity phenomena, some contribution of Taxol itself is possible. Anaphylaxis and angioedema have been reported in a teenager who chewed yew needles (45). Hypersensitivity reactions also occur in patients who receive Taxotere², a semisynthetic analogue of Taxol that is partially synthesized from 10-deacetylbaecatin III, isolated from the needles of the European yew, *Taxus baccata* (46). Taxotere is formulated with Tween-80, which has also been associated with hypersensitivity and skin reactions. At present, it is not possible to determine the rela-

tive contribution of the taxanes versus the diluents to the hypersensitivity reactions.

Preliminary toxicity analysis of a recently completed randomized trial comparing the 24- and 3-hour schedules, demonstrated that Taxol, with the routine premedication regimen, can be administered safely over 3 hours (47). Severe hypersensitivity reactions occurred in 2 of 47 patients (4%) on the 3-hour schedule and 1 of 66 patients (1.5%) on the 24-hour schedule.

Leukopenia. Phase I studies of Taxol demonstrated that leukopenia was frequent and dose limiting but that thrombocytopenia was rare. Doses of 200–250 mg/m² resulted in grades 3 and 4 myelosuppression in the majority of patients. Nevertheless, neutrophil counts generally recovered sufficiently rapidly to permit retreatment every 3 weeks.

Neurotoxicity. Because neutropenia was dose-limiting in phase I trials, granulocyte colony-stimulating factor (G-CSF) was added in an effort to increase Taxol dose (35). At doses above 250 mg/m² every 3 weeks, peripheral neuropathy, characterized primarily by sensory symptoms such as paresthesias and numbness in a stocking-glove distribution, became dose-limiting [discussed elsewhere in this monograph by Rowinsky et al. (40)]. Motor neuropathy has been reported following higher Taxol doses and in patients with other risk factors for neuropathy (48).

Because Taxol's target of drug action, the microtubule, is essential for normal nerve function, it seems unlikely that an analogue without neurological effects will be developed. Therefore, reports that nerve growth factor appears to block the neurotoxic effects of Taxol *in vitro* and in a murine model are exciting (49,50). Animal studies to ensure that nerve growth factor has no tumor-protective effects must be performed; however, because the taxanes are of great clinical interest, it is anticipated that nerve growth factor and related compounds will be important areas for future clinical evaluation.

Other Toxicities

Patients develop complete alopecia. Fatigue, arthralgia, and myalgia are common at the higher doses. Mucositis is also frequent at high doses and was dose limiting in a phase I trial in patients with refractory leukemia (recommended phase II dose of 315 mg/m² over 24 hours) and in a trial of Taxol administered by continuous infusion over 96 hours (34,51). Nausea, vomiting, and diarrhea occur infrequently. Toxicities associated with Taxol are summarized in Table 3 and discussed more extensively elsewhere in this monograph by Onetto et al. (52).

Cardiac toxicity and Taxol use in patients with cardiac risk factors. Because of concerns about life-threatening anaphylaxis early in Taxol's clinical development, investigators at Johns Hopkins Cancer Center performed continuous cardiac monitoring during Taxol infusion. Sinus bradycardia was documented in 29% of 40 patients but was rarely clinically significant (8). Other cardiac events were documented in 5% of 144 monitored patients (53). These events included heart block, nonsustained ventricu-

Table 3. Toxicities reported with Taxol*

Hematologic	Myelosuppression
Gastrointestinal	Nausea, vomiting, stomatitis, mucositis, pharyngitis
Heart	Arrhythmia, sinus bradycardia, heart block, nonsustained ventricular tachycardia, myocardial infarction
Blood pressure	Hypotension, hypertension
Neurologic	Peripheral neuropathy, sensory (taste), seizures, mood changes
Skin	Erythema, induration and discomfort following local infiltration; ulceration is rare
Hypersensitivity	
Major	Anaphylactoid reactions (acute), dyspnea, flushing, rash, urticaria, pruritus
Minor	
Other	Alopecia, fatigue, arthralgia, myalgia, light-headedness, myopathy

*Adverse Drug Reaction Database, Cancer Therapy Evaluation Program, National Cancer Institute, data on file.

lar tachycardia, other ventricular and atrial arrhythmias, myocardial ischemia, infarction, and electrocardiogram changes. The relationship between these events and Taxol was frequently uncertain. The reported incidence of cardiac events is much lower in patients who are not undergoing continuous cardiac monitoring because these events are often asymptomatic. [See discussion elsewhere in this monograph by Arbus et al. (54)].

Once cardiac events were reported, patients with potential cardiac risk factors were excluded from many clinical trials with Taxol in an effort to maximize the safety of patients receiving this investigational drug. Patients expected to be intolerant of bradycardia, including those with a history of congestive heart failure or angina, and those who had sustained a myocardial infarction within 6 months, were deemed ineligible. Patients with arrhythmias and those on medications known to alter cardiac conduction, including digoxin, calcium channel blockers, and beta adrenergic blockers, were also frequently excluded. (It is important to note, however, that upon review of the safety data in the Taxol New Drug Application [NDA], the Food and Drug Administration [FDA] did not implement these cardiac restrictions. Some of the data they reviewed, however, were obtained from studies that had these eligibility exclusions.) The actual risk associated with these clinical circumstances remains unknown.

Based on experience to date, patients without obvious risk factors do not require continuous cardiac monitoring. Insufficient data are available to make recommendations for those who have previously been excluded from most Taxol trials because of potential cardiac risk factors. Because many patients with cancer are elderly and have preexisting heart disease, additional research is warranted.

An Eastern Cooperative Oncology Group (ECOG) study with careful cardiac evaluation and monitoring will evaluate the risk of Taxol in some of these patient groups.

PHASE II CLINICAL TRIALS

Because the drug supply was limited when phase II trials began in 1985, initial studies were restricted to common tumor types and to disease settings in which responses had been observed (for example, melanoma, lung, and ovarian cancer) (28,36). The first important indication of clinical activity in a phase II trial was reported in women with recurrent and refractory ovarian cancer (8). These results were confirmed in three other phase II trials in refractory ovarian cancer and by the results of the NCI Treatment Referral Center Protocol TRC-9103 (55-58).

Activity in breast cancer was first reported in 1991, in lung cancer and head and neck cancer in 1992 (9-12,59). Table 4 summarizes the results of completed phase II clinical trials. A more detailed discussion of the utility of Taxol in ovarian, breast, lung, and head and neck cancer patients and in melanoma, appears elsewhere in this monograph (64a-e). Preliminary data from a trial evaluating Taxol administered by 4-day continuous infusion suggest that the drug may have activity in patients with refractory lymphoma (51), and additional single-agent trials with the 24-hour infusion regimen are ongoing.

Taxol was inactive in phase II trials in renal, colon, and prostate cancer (48,60,61). Response rates of 10% to 14%

were reported in cancer of the cervix and melanoma (48,62,63) (Table 4). In keeping with standard drug development approaches, a second trial is being performed in those tumor sites where only one trial has been completed; in most cases, higher doses are being studied. In vitro, prolonged drug exposure has been associated with enhanced drug retention in tumor cells with the multidrug-resistant (MDR) phenotype and with increased cytotoxicity (65). Thus, the 96-hour infusion is being evaluated in colon carcinoma, a tumor thought to be associated with the MDR phenotype *de novo*.

Table 5 lists disease sites for ongoing phase II trials. Results from these trials are not yet available.

Limited Supply of a Scarce Natural Product

Clinical development of Taxol, with its complex pharmaceutical and therapeutic considerations, was hampered by additional problems. The initial source of Taxol was the bark of the Pacific yew, *T. brevifolia*, a small, slow-growing species that previously was discarded during lumber harvests. Until recently, the yield of Taxol from *T. brevifolia* bark averaged 0.01% by weight, providing approximately 1 kg of clinical grade drug for every 20 000 pounds of bark (5). Each tree yielded enough drug (1 g) to provide only two to three average doses of Taxol. As much as 20 kg of Taxol would be required to treat the 12 000 women who die each year of ovarian cancer. Recent improvements in Taxol production technology are more efficient and annual Taxol production capacity is approaching 230 kg (66).

Table 4. Phase II trials

Disease	Institution (starting dose*)	Evaluable	CR	PR	% Objective response	Reference
Ovary	Hopkins (200, 250→ 135, 170) [†]	40	1	11	30	(8)
	Einstein (250) [‡]	30	1	5	20	(56)
	GOG [§] (170)	41	5	10	37	(55)
	NCI Medicine Branch (250)	38	0	19	50	(57)
	TRC [¶] /NCI (135)	348	14	80	24	(58)
Breast	M. D. Anderson (200, 250) [‡]	25	3	11	56	(9)
	Memorial (250) [‡]	26	1	15	62	(50)
Non-small-cell lung	M. D. Anderson (200)	25	1	5	24	(10)
	ECOG [#] (250)	24	0	5	21	(11)
Melanoma	ECOG (250)	28	3	1	14	(63)
	M. D. Anderson [†] (200, 250)	25	0	3	12	(62)
Renal	Einstein [‡] (250)	18	0	0	0	(61)
Prostate	ECOG (135,170)	22	0	1	4	(60)
Colon	ECOG (250)	19	0	0	0	(48)
Cervix	GOG (135, 170)	30	0	3	10	(48)

*24-hr infusion schedule unless noted otherwise. When two doses are indicated: poor risk, good risk.

[†]70% of courses were administered at ≤ 135 mg/m².

[‡]>55% of patients had dose reduction to 200 mg/m² most often because of febrile neutropenia.

[§]Gynecologic Oncology Group.

^{||}With G-CSF.

[¶]Treatment Referral Center.

[#]Eastern Cooperative Oncology Group.

Table 5. Ongoing phase II trials

Esophagus	Small-cell lung
Stomach	Leukemia
Pancreas	Lymphoma
Hepatoma	Multiple myeloma
Bladder	Brain
Germ cell	Neuroendocrine
Endometrium	Pediatric tumors
Sarcoma	

Once anticancer activity was reported in women with refractory ovarian cancer, it became apparent that a larger Taxol supply would be required to expand the phase II studies, to develop drug combinations, to initiate phase III trials, and to make the drug available on a compassionate basis. To meet these needs, alternate sources of Taxol were required.

NCI convened the first workshop on Taxol and *Taxus* in 1990 and brought together chemists, botanists, forestry experts, pharmacologists, and oncologists from industry, academia, and government to focus attention on this important drug. Significant progress in the development of alternate Taxol sources was reported at this second workshop, in part, due to initiatives that followed the first meeting.

In 1989, NCI also advertised in the *Federal Register* for a pharmaceutical partner. In January 1991, after an open competition, a Collaborative Research and Development Agreement (CRADA) between Bristol-Myers Squibb and NCI was signed. Elsewhere in this monograph, DeFuria and Horovitz discuss the responsibilities of the two parties in subsequent Taxol development (67). Bristol-Myers Squibb was responsible for supplying Taxol for clinical trials and compassionate use and for speedily filing an NDA. Table 6 documents the remarkable expansion of the clinical trials program that resulted from the increased Taxol supply produced by Bristol-Myers Squibb after the CRADA was signed.

The increased drug supply also permitted NCI to initiate a Treatment Referral Center protocol for women with refractory ovarian cancer in September 1991, and for refractory breast cancer in October 1992. The NDA for Taxol was submitted to the FDA by Bristol-Myers Squibb in July 1992 and reviewed by the FDA Oncologic Advisory Committee in November 1992. The committee unanimously recommended approval of Taxol as second-line therapy for ovarian cancer in November 1992 and the NDA was approved by the FDA in December 1992.

Semisynthetic Taxol produced from 10-deacetylbaccatin III, a precursor isolated from yew trees in Europe and India and from needles and twigs from ornamental yew shrubs, is expected to become available in bulk in 1993. The development of this semisynthetic product from a renewable source will eradicate the need for harvesting yew from old-growth forests. Taxol production from other renewable sources is also under development. Approaches include complete chemical synthesis from pinene, a major component of inexpensive industrial sol-

Table 6. Taxol clinical trials

Date	Number of active trials
1983-1990	21
Jan 1991	9
Jan 1992	16
July 1992	36
Dec 1992	54*

*16 additional submitted protocols in CTEP review process.

vents such as turpentine (68) and plant cell culture. Development of Taxol analogues such as Taxotere² is another active area of research (69,70).

Treatment Referral Center Protocol

The NCI Treatment Referral Center was established to provide access to active investigational drugs to patients with disease refractory to conventional therapy. Thirty-nine NCI-designated clinical comprehensive cancer centers participated in a program that began in September 1991. Patients with refractory ovarian cancer who had received a minimum of three prior chemotherapy regimens (two as of July 1992), with ECOG performance status 0-3, absolute granulocyte counts $\geq 2000/\mu\text{L}$, creatinine $< 3 \text{ mg\%}$, bilirubin $\leq 2 \text{ mg\%}$, and no cardiac risk factors were registered for treatment. A Taxol dose of 135 mg/m^2 was administered by 24-hour infusion every 3 weeks. G-CSF was added in subsequent cycles if patients developed febrile neutropenia, white blood count (WBC) less than $1000/\mu\text{L}$ for more than 7 days, or if WBC had not recovered in time for retreatment on day 22.

Between September 1991 and September 1992, 1700 patients were registered. Preliminary data for the first 500 patients, all registered prior to January 15, 1992 and with minimum follow-up of 10 months, are presented here (58). Four hundred and eighty treated patients received 2485 courses (median of five cycles per patient; range 1-17). Thirty-nine percent of patients received G-CSF. Nine percent had dose reductions, and 26% required treatment delay of greater than 1 week. Grades 3 and 4 leukopenia occurred in 82%, and fever was reported in 33%. The incidence of severe and life-threatening infections was 10% and 5%, respectively. Severe toxicities of other types, including neurotoxicity, hypersensitivity, and cardiac toxicity were infrequent. Eight of 480 treated patients (1.6%) died with treatment-related toxicity. Seven of these deaths were associated with febrile neutropenia, and most occurred after the first treatment.

Among the first 500 patients, 348 had measurable disease and were evaluable for response. The complete and partial response rates were 4% and 20%, respectively. Sixteen percent of patients had stable disease. The 95% confidence interval for objective response was 20% to 29%. Median time to progression was 7 months for patients with responses and 4 months for all treated patients. Median survival for the entire study population was 9 months. These response and survival results in patients

who had received three or more prior treatment regimens confirm earlier reports that Taxol is associated with clinical benefit in advanced refractory ovarian cancer. In addition to providing Taxol to patients without other effective therapeutic options, the Treatment Referral Center program provided additional safety and response information prior to Taxol's approval by the FDA.

Other Drug Development Issues

Schedule. As discussed previously, the 24-hour infusion schedule was utilized in phase II trials because it was associated with a lower incidence of hypersensitivity reactions and with responses in phase I trials. Recently, however, Eisenhauer et al. reported preliminary safety analysis of a phase III randomized trial with a factorial design that evaluated the 3- and 24-hour schedules, each with two Taxol doses, 135 and 175 mg/m² (47). Preliminary safety analysis documented that Taxol can be administered safely on the 3-hour schedule when the three-drug premedication regimen is used.

This study also demonstrated that neutropenia was schedule dependent. The 24-hour schedule was associated with more neutropenia than the 3-hour schedule, at both doses. Whether the long infusion schedule will also be associated with improved efficacy is unknown at this time. Nonetheless, it is possible that higher, equitoxic doses administered over 3 hours would be more effective than the highest dose (175 mg/m²) evaluated in this study. A phase I trial to determine the maximally tolerated dose of Taxol on a 3-hour schedule is nearing completion (Schiller J, Spriggs D, personal communication). Other schedules, including a 96-hour infusion schedule, which was developed because of encouraging preclinical data documenting improved efficacy with prolonged exposure, are also undergoing clinical testing (51). Randomized phase III trials are necessary to determine if longer infusion schedules are associated with improved efficacy, or if the more convenient 3-hour schedule should be adopted routinely.

Optimal dose. McGuire et al., who first reported Taxol activity in ovarian cancer, administered Taxol 250 mg/m² to patients who had received one prior chemotherapy regimen and 200 mg/m² to those who had received more than one prior regimen or extensive radiation therapy (8). As a consequence of nadir leukocyte counts, starting doses were soon reduced to 170 mg/m² with further reductions to 135 mg/m² in some heavily pretreated patients. Subsequent doses were decreased in patients who developed grade 4 hematologic toxicity (WBC <1000/ μ L or leukocytes <500/ μ L). Of 281 courses, 62 were administered at 110 mg/m², 135 at 135 mg/m², 61 at 170 mg/m², 19 at 200 mg/m², and only 4 at 250 mg/m². Eleven of 40 evaluable patients responded to treatment (30%). These investigators reported no correlation between the average administered dose of Taxol and the likelihood of response.

Based on these findings and the results of a phase I trial demonstrating that Taxol 135 mg/m² could be combined safely with cisplatin 75 mg/m² (71), the Gynecologic Oncology Group (GOG) adopted this regimen for their phase III clinical trials in ovarian cancer. The 175 mg/m²

dose is being evaluated in ovarian cancer by Bristol-Myers Squibb in trials in Canada and Europe and is well tolerated without G-CSF. Because responses were documented in ovarian cancer patients who received the 135 mg/m² dose and because there is no documentation yet that more is better, the FDA approved the 135 mg/m² dose.

With adequate supplies of Taxol assured, and to maximize the likelihood of identifying activity, the Cancer Therapy Evaluation Program (CTEP) decided to utilize the 250 mg/m² dosage with G-CSF in subsequent phase II solid tumor studies. Phase II screening of new anticancer drugs in combination with G-CSF is not routine and documentation of activity does not prove that the higher dose with the addition of G-CSF is necessary. Higher doses with G-CSF were used to avoid any possibility of missing activity because of inadequate dosing. The issue of the importance of dose intensity is being addressed definitively in phase III trials.

Without G-CSF, McGuire and others have demonstrated that a dose of 250 mg/m² is not generally tolerable for multiple courses due to neutropenia, neurotoxicity, myalgias, arthralgias, and fatigue, and most patients have required dose reductions (8,9). Patients without extensive prior therapy usually tolerate repeated courses at 200 or 180 mg/m² (9). More than 50% of patients with breast cancer who received starting doses of Taxol 250 mg/m² with G-CSF required dose reductions to 200 mg/m² by course 3 (Reichman B, Seidman A, and Norton L, personal communication). Whether G-CSF is administered or not, bone marrow recovery generally occurs by day 22, permitting retreatment on a 3-week schedule.

Addition of G-CSF does not result in a large difference in administered dose intensity or median nadir granulocyte count; however, the use of G-CSF does shorten the duration of severe neutropenia from approximately 4–6 days to 2–4 days (9,59). It is known that as duration of neutropenia increases, the risk of infection also increases (72). The incidence of infection was similar in two breast cancer trials with and without G-CSF, but definitive comparisons are not possible in two small nonrandomized phase II trials (9,59).

Dose reductions for hematologic toxicity based on a single nadir count have been standard practice for many years. Recently, for some studies, CTEP encouraged criteria incorporating the clinical outcome associated with neutropenia. Most Taxol trials required dose reductions for leukopenia only if patients developed febrile neutropenia or prolonged neutropenia. These criteria for dose reduction permit administration of higher Taxol doses.

It is clear that if the patient accepts additional toxicity including neurotoxicity, myalgia, arthralgia, and fatigue, the physician can administer a higher Taxol dose. It is not clear, however, that this approach increases response rate or prolongs survival. A randomized trial to determine whether higher Taxol doses are associated with clinical benefit is being conducted by the Gynecologic Oncology Group. Patients who have progressive ovarian cancer following platinum-based therapy are randomized to receive either Taxol 135 mg/m², Taxol 175 mg/m², or Taxol 250

mg/m². Patients on the highest dose are randomized to receive either 5 or 10 µg/kg of G-CSF. Another trial, in non-small-cell lung cancer patients, will also address the Taxol dose question, but in combination. Patients are randomized to receive either Taxol 250 mg/m² with G-CSF, Taxol 135 mg/m², or on the "standard" arm, etoposide. In each arm cisplatin is administered at a dose of 75 mg/m². When the importance of schedule became apparent, a pivotal trial was designed to examine effects of both dose and schedule in patients with breast cancer. It is expected that half the patients will receive Taxol over 3 hours and the remaining patients will be treated over 24 hours. Ideally, the maximally tolerated dose with and without G-CSF will be evaluated for each schedule.

In addition to the previously mentioned Canadian/European trial in ovarian cancer, two other trials are expected to provide additional insights on dose and schedule. Both trials are performed under Bristol-Myers Squibb sponsorship in patients with advanced breast cancer. The first trial, recently closed to accrual, compared doses of 175 and 135 mg/m² administered over 3 hours. The second trial, currently ongoing, compares doses of 175 mg/m² administered over 24- or 3-hour infusion. The results of all of these trials are expected to help identify the optimal single-agent Taxol dose and schedule.

Combination therapy. The best therapeutic results in cancer chemotherapy are usually achieved with combinations of two or more drugs. When possible, efforts are made to combine full doses of non-cross-resistant drugs with single-agent activity, differing mechanisms of action, and nonoverlapping toxicity. Because Taxol is most frequently associated with partial, but not complete, responses (Table 4), identification of effective drug combinations is an important goal. With its unique mechanism of action, Taxol provides both opportunities and challenges for development of combination chemotherapy. Usually, combination regimens are developed empirically. As more is understood about mechanisms of drug action, drug interactions, and biochemical pharmacology and as preclinical model systems are developed, rationally designed combinations become possible. Preclinical studies of Taxol in combination with other agents began late, primarily because of Taxol's limited supply. Nevertheless, some data are currently available.

In a subcutaneously implanted murine lung cancer model (Madison 109), no increase in lifespan greater than that achieved with Taxol alone was obtained when Taxol was administered in combination with cisplatin, etoposide, doxorubicin, or cyclophosphamide (73). In murine 16/C and human MCF7 mammary adenocarcinoma models, superadditive activity was demonstrated with doxorubicin pretreatment and subadditive activity with concomitant administration or Taxol pretreatment (74). For Taxol combined with topotecan, there was additive activity in MCF7 when topotecan was administered first and subadditive activity with Taxol pretreatment. The results differed in 16/C cells where superadditive activity was observed for both sequences.

Taxol was studied in mice in combination with doxorubicin or 5-fluorouracil and in the three-drug combination of cyclophosphamide, doxorubicin, and Taxol (75). An alternating schedule of Taxol and doxorubicin, with each drug administered every 4 days resulted in synergy with acceptable toxicity. The results with Taxol and doxorubicin were similar to those obtained with the three-drug combination. The Taxol/doxorubicin combination resulted in log cell kill of 6.2 compared with 4.6 for Taxol and 3.6 for doxorubicin alone. The combination of Taxol and 5-fluorouracil was not superior to Taxol alone (75). Antagonism was reported when Taxol was combined in vitro with doxorubicin, etoposide or m-amsa in human breast MCF-7, lung A549, and ovarian OVG-1 adenocarcinoma cell lines (76).

The challenge of combining Taxol with other drugs is even more complex when the second drug also targets microtubules. The combination of a drug that stabilizes microtubules with one that destabilizes them could prove antagonistic with less anticancer activity or substantially more cytotoxic with adverse effects also manifested in normal host cells.

It is not yet known whether in vivo or in vitro systems will reliably predict optimal combinations and sequences. Many combination studies with Taxol were initiated before preclinical data were available, hence, these clinical studies were empirically designed to explore several schedules, dosages, and sequences.

Following the initial promising clinical activity in ovarian cancer, a phase I evaluation of the combination of Taxol with cisplatin was initiated. Preclinical data were available for this combination. Taxol followed by cisplatin resulted in maximal cytotoxicity in L1210 cells (77). In the phase I trial, this sequence also resulted in less myelotoxicity (71). Furthermore, the reverse sequence was associated with decreased Taxol clearance. Cisplatin's effect on the P450 system may account for the resulting decreased clearance of Taxol (78). Based on these results, Taxol 135 mg/m², followed by cisplatin 75 mg/m², was recommended for further evaluation (71). A phase III trial, GOG 111, randomly allocated women with suboptimally debulked ovarian cancer to this investigational combination or to the standard GOG regimen, cyclophosphamide 600 mg/m², and cisplatin 75 mg/m². The results of this important study were presented at the American Society of Clinical Oncology Meeting in May 1993.

Two studies of different schedules of Taxol and doxorubicin administered by continuous infusion have been reported (79,80) and alternate schedules are being explored. Pilot studies of other Taxol combinations are ongoing to develop treatment regimens for phase III evaluation in ovarian, breast, lung, and head and neck cancer. Ongoing Taxol combination trials include studies with carboplatin, cyclophosphamide, edatrexate, etoposide, 5-fluorouracil ± leucovorin, ifosfamide, methotrexate, and topotecan.

Radiation sensitization. Taxol concentrations as low as 10 to 100 nM/L enhanced the effects of ionizing radiation in the relatively radioresistant G18 astrocytoma cell line

(81). The degree of enhanced cell killing depended on Taxol concentration and the fraction of cells in G₂ or M phases of the cell cycle. Because Taxol blocks cells in G₂/M, and cells in G₂/M are more sensitive to radiation, radiation sensitization has been attributed to the kinetic perturbation induced by Taxol (81). In MCF-7 human breast and Shaw pancreatic adenocarcinoma cell lines, however, Taxol concentrations of 1–10 nM, which were sufficient to induce G₂/M block, did not increase the effectiveness of radiation (82). Higher Taxol concentrations did enhance radiation sensitivity in these two cell lines. A549 human lung adenocarcinoma cells were not sensitized to radiation by Taxol at any concentration tested. Thus, the mechanism for radiation sensitization remains incompletely understood. Further, *in vivo* experimental data would be of interest.

The combination of radiotherapy and Taxol has potential application in several tumor types, including breast, head and neck, and non-small-cell lung cancer. Phase I studies of radiation therapy in combination with Taxol administered on a variety of schedules are underway. Phase II trials are anticipated.

Resistance. Taxol is a hydrophobic natural product. These characteristics are often associated with induction of the MDR phenotype. A highly resistant cell line selected from Taxol-sensitive murine tumor macrophage J774.2 cells displays the MDR phenotype and overproduces P-glycoprotein, an energy-dependent drug efflux pump that maintains intracellular drug concentrations below cytotoxic levels (16). Whether this observation is pertinent in the clinic is not known. Because some agents can ameliorate Taxol resistance mediated by MDR *in vitro* in cells with the MDR phenotype (83), phase I trials of Taxol in combination with R-verapamil, quinine, and cyclosporin are underway. Interestingly, the Cremophor EL, in which Taxol is formulated, has been shown to overcome MDR in some systems (84).

The contribution of MDR to Taxol insensitivity in patients is not defined, however. Two groups have documented objective responses to Taxol in small numbers of patients who had tumors that progressed during or soon after doxorubicin treatment (9,85). These reports may not be surprising because multiple mechanisms are responsible for drug resistance. Several clinical trials that incorporate pretreatment tumor biopsy for determination of MDR may contribute to an understanding of the role of MDR in patients treated with Taxol. Other large randomized studies in breast cancer with cross-over designs may permit determination of the incidence of cross-resistance to Taxol and MDR-inducing drugs, such as doxorubicin and vinblastine (Table 7).

When other antimetabolic drugs are used to select resistant Chinese hamster ovary (CHO) cells in the laboratory, the majority of mutant cells demonstrate the MDR phenotype. With Taxol selection, most of the mutant cells have tubulin alterations which decrease microtubule assembly (86). Cells with this mechanism of Taxol resistance may exhibit increased sensitivity to drugs such as colchicine and vinblastine that act to destabilize microtubules (87).

Taxol-resistant CHO cells have been developed with altered α - or β -tubulin (88) or with a normal cytoplasmic microtubule complex but impaired ability to form a mitotic spindle in the absence of Taxol (89).

Taxol induced the formation of multiple asters in G₂/M and bundling of microtubules throughout the cell cycle in both sensitive and resistant human leukemia cell lines (15,16). Multiple aster formation was reversible and not significantly associated with cytotoxicity in all cell lines examined. In contrast, microtubule bundling was associated with cytotoxicity, and it was reversible in the resistant cells but irreversible in the sensitive cells. Microtubule bundling persisted following treatment even when the sensitive cells were placed in Taxol-free media. Resistant cells also had greater DNA polyploidy than sensitive cells (90).

Multiple mechanisms of drug resistance are common with other agents; one would anticipate that multiple mechanisms of resistance to Taxol will also be identified in human tumors. Studies that assess mechanisms of resistance in human samples, and cloning and sequencing of genes associated with resistance may help determine the molecular basis for Taxol resistance in human tumors. Some studies in patients with clinically accessible tissue, for example, leukemia, multiple myeloma, and head and neck tumors, have incorporated evaluation of possible markers of drug response or resistance which can now be studied. These include MDR phenotype and microtubule bundling.

Use in patients with abnormal liver function. Early in a new drug's development, investigational use is often restricted to patients with relatively normal organ function. In clinical practice, many cancer patients have impaired hepatic function. As previously described, studies in rodents and in one patient documented Taxol metabolites in bile and suggested that hepatic metabolism plays an important role in Taxol clearance (41,42). With evidence of increasingly broad clinical activity, a phase I trial was initiated to evaluate the toxicity and pharmacokinetics of Taxol in patients with abnormal liver function. This study will determine whether Taxol can be used safely in patients with hepatic impairment and, if so, determine necessary dose adjustments.

PHASE III TRIALS

Table 7 describes completed, active, and planned NCI-sponsored phase III trials. The first, in suboptimally debulked stage 3 and 4 ovarian cancer, completed accrual in March 1992. A second-generation study is ongoing in this group of patients, and studies in optimally debulked and platinum refractory disease are accruing patients. Three phase III trials in breast cancer and a phase III trial in non-small-cell lung cancer will begin in early 1993. An adjuvant trial in breast cancer is expected to begin in 1993. Table 8 describes Bristol-Myers Squibb sponsored phase III trials, one in ovarian cancer and two in breast cancer.

Table 7. NCI-sponsored phase III trials

Ovary		
Suboptimally debulked, no prior chemotherapy		
GOG*111 (completed 3/92)	versus	Cisplatin 75 mg/m ² + cyclophosphamide 750 mg/m ² Cisplatin 75 mg/m ² + Taxol 135 mg/m ²
GOG 132 (activated 3/92)	versus	Cisplatin 75 mg/m ² + Taxol 135 mg/m ² Cisplatin 100 mg/m ²
	versus	Taxol 200 mg/m ²
Optimally debulked, no prior chemotherapy		
GOG 114 (activated 7/92)	versus	Cisplatin 75 mg/m ² + cyclophosphamide 750 mg/m ² Cisplatin 75 mg/m ² + Taxol 135 mg/m ²
	versus	Carboplatin × 2 courses then intraperitoneal cisplatin + Taxol 135 mg/m ²
Platinum resistant		
GOG 134 (activated 7/92)	versus	Taxol 135 mg/m ² Taxol 175 mg/m ²
	versus	Taxol 250 mg/m ² + G-CSF (5 versus 10 µg/kg/d)
Breast		
No prior chemotherapy for metastatic disease		
ECOG† (planned)	versus	Taxol Doxorubicin
	versus	Taxol + doxorubicin (if suitable combination regimen is developed) (Patients on single-agent arms crossover at progression)
Symptomatic patients with measurable disease		
Refractory to doxorubicin		
Planned		
Treatment Referral Center	versus	Taxol 210 mg/m ² (3 hr) every 3 weeks Vinblastine 5.5 mg/m ² weekly (Patients cross over at progression)
Metastatic breast cancer		
Planned	versus	Taxol 175 mg/m ² (24 hr) Taxol 250 mg/m ² (24 hr) + G-CSF
	versus	Taxol 210 mg/m ² (3 hr)
	versus	Taxol 250 mg/m ² (3 hr) + G-CSF
Non-small-cell lung cancer		
No prior chemotherapy		
Planned	versus	Cisplatin 75 mg/m ² + Taxol 135 mg/m ² Cisplatin 75 mg/m ² + Taxol 250 mg/m ² + G-CSF
	versus	Cisplatin 75 mg/m ² + VP16

*Gynecologic Oncology Group.

†Eastern Cooperative Oncology Group.

Table 8. Bristol-Myers Squibb sponsored phase III trials

Ovary		
Platinum resistant		
BMS 015 (NCIC OV9) (completed 3/92)	versus	Taxol 135 mg/m ² (3 h) Taxol 135 mg/m ² (24 h)
	versus	Taxol 175 mg/m ² (3 h)
	versus	Taxol 175 mg/m ² (24 h)
Breast		
≤1 prior chemotherapy for metastatic disease		
BMS 048 (completed 8/92)	versus	Taxol 135 mg/m ² (3 h) Taxol 175 mg/m ² (3 h)
≤1 prior chemotherapy for metastatic disease		
BMS 071 (activated 9/92)	versus	Taxol 175 mg/m ² (3 h) Taxol 175 mg/m ² (24 h)

CONCLUSIONS

Taxol is a prototype for a new class of anticancer drug which has focused attention on tubulin and microtubules as critical targets for chemotherapy. Taxol's unique effects include its ability to polymerize tubulin into stable microtubules in the absence of cofactors and to induce the formation of stable microtubule bundles. The site at which Taxol causes cytotoxicity, however, is poorly understood as are its interactions with other factors affecting microtubules. Mechanisms of *de novo* and acquired Taxol resistance in human tumors are not well defined. As some of these questions are resolved, our ability to exploit this important new drug in the clinic should increase.

Numerous formidable challenges have been overcome: a suitable formulation was developed, an adequate supply was ensured, severe hypersensitivity reactions were diminished in incidence and severity, clinical efficacy was demonstrated, and FDA approval was granted. The current clinical challenges include continued identification of tumor types for which the drug has activity, determination of optimal dose and schedule, and integration of this agent with its novel mechanism of action into effective combination regimens for treatment of breast, ovary, lung, and head and neck cancer. There are few preclinical leads for development of combinations that are more effective than single agent Taxol. Important areas of current investigation include combinations of Taxol with radiation and with other drugs. Effective combinations are required for additional evaluation in earlier stages of disease in women with breast and ovarian cancer. Further evaluation of Taxol in pediatric tumors is required. Phase I trials have been completed and phase II trials initiated in pediatric patients with leukemia and solid tumors. Studies are underway to assess whether Taxol can be safely administered to patients with abnormal liver function and to those with potential cardiac risk factors.

Over the past 30 years, many individuals have contributed to the accomplishments summarized here. Ongoing and future studies designed to address the remaining questions are expected to help optimize Taxol use and permit us to incorporate this important compound, the first of a new class of anticancer agents, more effectively into clinical practice.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

²Taxotere is used in this monograph to refer to the drug that now has the generic name docetaxel and the registered trade name Taxotere® (Rhône-Poulenc-Rorer Pharmaceuticals Inc., Collegeville, Pa.).

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Clinical Pharmacology of Taxol

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Taxol is the first novel antimicrotubule agent approved for clinical use since the vinca alkaloids in the 1960s and may be one of the most important antineoplastic agents to emerge over the last two decades. Significant antitumor activity has been noted in ovarian, breast, lung, and head and neck cancers. This report reviews the clinical pharmacology of Taxol based on early developmental trials of the agent administered on various intravenous schedules as a single agent and in combination with other antineoplastic agents, as well as via the intraperitoneal route. In addition, available information pertaining to the pharmacodynamic and metabolic profiles of Taxol are discussed. Such information may be useful in designing rational treatment approaches with Taxol either as monotherapy or in chemotherapy combinations, potentially resulting in the optimal use of this important agent in cancer chemotherapeutics. [Monogr Natl Cancer Inst 15:25-37, 1993]

Taxol¹, the prototypic taxane antimicrotubule agent that induces tubulin polymerization and stabilizes microtubule polymers, is the first compound in its class to demonstrate significant clinical antineoplastic activity. To date, impressive activity has been observed in patients with breast, lung (non-small-cell and small-cell), head and neck, and advanced and platinum-refractory ovarian carcinomas (1-11). Although the structural identification of Taxol was first reported in 1971 (12) and extensive preclinical screening and toxicologic studies were performed in the early 1980s (reviewed in 13), there was a lack of detailed pharmacologic information available when Taxol entered National Cancer Institute (NCI)-sponsored clinical trials in 1983. This was due, in part, to Taxol's aqueous insolubility, which hampered the development of suitable analytical assays, as well as to the inherent insensitivity of available analytical methods in measuring the complete range of concentrations achieved in small animals. When available, such information is often useful in designing rational treatment schedules for clinical evaluation. Therefore, most pharmacologic data pertaining to Taxol were obtained during clinical studies performed over the last decade. This report summarizes current information pertaining to the pharmacologic, pharmacodynamic, and metabolic behavior of Taxol.

ANALYTICAL METHODS

When Taxol entered phase I clinical development, minimal relevant preclinical data were available pertaining to the agent's behavior in vivo. Although several analytical assay methods were described before Taxol entered phase I clinical development, these assays were generally tedious, insensitive, and applicable for neither preclinical nor clinical pharmacologic studies. For example, Hamel et al. described a unique biochemical assay with a sensitivity of 0.1 $\mu\text{mol/L}$, which exploited the ability of Taxol to induce tubulin to form cold-resistant polymers that hydrolyze guanosine-5'-triphosphate (GTP) at 0°C (14). Several reverse-phase high-performance liquid chromatographic (HPLC) methods were subsequently developed during early phase I trials to measure Taxol concentrations in biological samples (15-23). Using basically similar drug extraction and analytical methods, these HPLC assays permitted the characterization of the pharmacokinetic behavior of Taxol on many administration schedules. However, the variable extraction efficiencies and lower limits of sensitivity of most of the earlier HPLC assays (0.05 $\mu\text{mol/L}$) rendered them suboptimal, especially for monitoring large numbers of patients receiving lower doses of Taxol administered on relatively long infusion schedules (e.g., 24 hours). Recently, Wall et al. described a modified HPLC assay that appears to be more sensitive compared with earlier procedures (24). This procedure employs a substantially longer analytical column. In addition, Huizing et al. recently described a highly sensitive HPLC assay with a lower limit of detection of 0.007 and 0.009 $\mu\text{mol/L}$ in plasma and urine, respectively (25). In addition, various immunological methods appear quite promising with respect to sensitivity, specificity, and overall clinical applicability (26-28). These immunological methods include rapid and sensitive indirect competitive inhibition enzyme immunoassays (CIEIA) (26,27) and competitive enzyme-linked immunosorbent assays (ELISA) (28). Immunological assays were principally developed for quantitating taxanes in plant extracts. The CIEIA, which appears to be much more sensitive (0.3 nmol/L) than available HPLC methods, may be useful in monitoring Taxol concentrations achieved in patients participating in large clinical trials, particularly those employing longer infusion schedules. Although the original CIEIA utilized polyclonal antisera, a CIEIA that uses a monoclonal antibody directed against the taxane ring has recently been developed and may be considerably more sensitive than the monoclonal technique (27; Grothaus P: personal communication).

*See "Notes" section following "References."

PHARMACOKINETICS

The only pharmacologic data available prior to early phase I evaluations of Taxol were limited to information provided by Hamel et al. using the biochemical assay discussed in the previous section (14). These investigators demonstrated that Taxol was almost entirely bound to plasma proteins (92%) in rabbits; however, the agent was readily cleared from the plasma compartment. Hamel et al. noted that the disappearance of Taxol in plasma was biphasic, with α and β half-lives of 2.7 and 45 minutes, respectively, when Taxol was administered as a rapid intravenous bolus to a single rabbit. The pharmacokinetic behavior of Taxol has been studied during early phase I investigations (13–21). The majority of these studies employed longer 6- and 24-hour infusion schedules due to the high incidence of major hypersensitivity reactions associated with shorter infusions during early clinical trials. Table 1 summarizes several pertinent pharmacokinetic parameters derived from early phase I trials that have been published previously. Although substantial interpatient variability was noted in early trials, there was clear evidence for neither nonlinear nor dose-dependent behavior over relatively broad dose ranges, particularly with longer (6- and 24-hour) infusion schedules. Instead, both peak plasma Taxol concentrations and areas under concentration-versus-time curves (AUC) have generally correlated well with dose (13–15,18). Taxol's disposition in plasma has been characterized by a biexponential model of drug elimination in all early studies. Typical plasma disappear-

ance curves are displayed in Fig. 1. Mean α and β half-lives derived from these studies have ranged from 0.27 to 0.49 hours (cumulative mean, 0.34 hours) and 1.3 to 8.6 hours (cumulative mean, 4.9 hours), respectively, and mean residence times have ranged from 5.6 to 19.9 hours (cumulative mean, 11.5 hours). Plasma disposition data of some patients participating in more recent studies using more sensitive HPLC assays have all been well described by triphasic models (25,29,30). For example, Huizing et al. have reported on preliminary pharmacologic results using 3-hour infusions and a highly sensitive HPLC assay in which the disposition of Taxol in plasma was optimally modeled by a three-compartment model (25). The half-lives were reported to be 10 minutes (α), 2 hours (β), and 15 hours (γ).

Recently, there has been a resurgence of interest in shorter 3-hour infusion schedules since a joint National Cancer Institute of Canada Clinical Trial Group-European study in previously treated patients with ovarian cancer demonstrated that the incidence of major hypersensitivity reactions is low and, more important, equivalent, in patients receiving Taxol over either 3 hours or 24 hours following premedication with high doses of corticosteroids, H₁- and H₂-histamine antagonists (31). Antitumor activity was also found to be equivalent on both schedules. From a pharmacologic perspective, preliminary results of these studies indicate that Taxol pharmacokinetics may be nonlinear, especially when the agent is administered over 3 hours, with mean peak plasma Taxol concentrations (C_{\max}) and AUC increasing disproportionately with increasing Taxol doses (25, 29–34). These findings do not necessarily differ from the results of earlier

Table 1. Early studies using prolonged infusion Taxol schedules: Taxol pharmacokinetic parameters

Schedule	Model	Half-life (h)		Systemic clearance (mL/min/m ²)	Peak plasma concentration (μ M) (dose, mg/m ²)	Volume of distribution at steady-state	Mean residence time (h)	Urine (% dose)
		α	β					
6-h infusion (San Antonio) (15)	Biphasic	0.49	4.3	232	2.0–6.7 (175–275)	48.5	11.8	8.2
6-h infusion (Einstein) (16)	Biphasic	0.32	8.6	100	3.2–8.1 (175–275)	55	8.6	5.2
24-h infusion (Einstein) (17)	Biphasic	0.27	3.9	993	0.6–0.94 (200–275)	182	19.9	1.4
1–6-h infusion q d \times 5d (Wisconsin) (18)	Biphasic	—	1.3	833	0.06–0.37 (15–40)	81	—	6.6
1–6-h infusion (Hopkins) (20)	Biphasic	0.27	6.4	253	1.3–13.0 (60–265)	67	5.6	5.9
24-h infusion (Hopkins) (21)	—	—	—	—	1.6–3.5 (250–390)	—	—	—
24-h infusion + cisplatin (Hopkins) (22)	—	—	—	—	0.21–0.83 (110–200)	—	—	—
24-h infusion + cisplatin + G-CSF (Hopkins) (23)	—	—	—	—	0.52–3.4 (135–350)	—	—	—
Mean (SD)	—	0.34 (0.09)	4.9 (2.7)	482 (402)	—	87 (55)	11.5 (6.2)	5.5 (2.5)

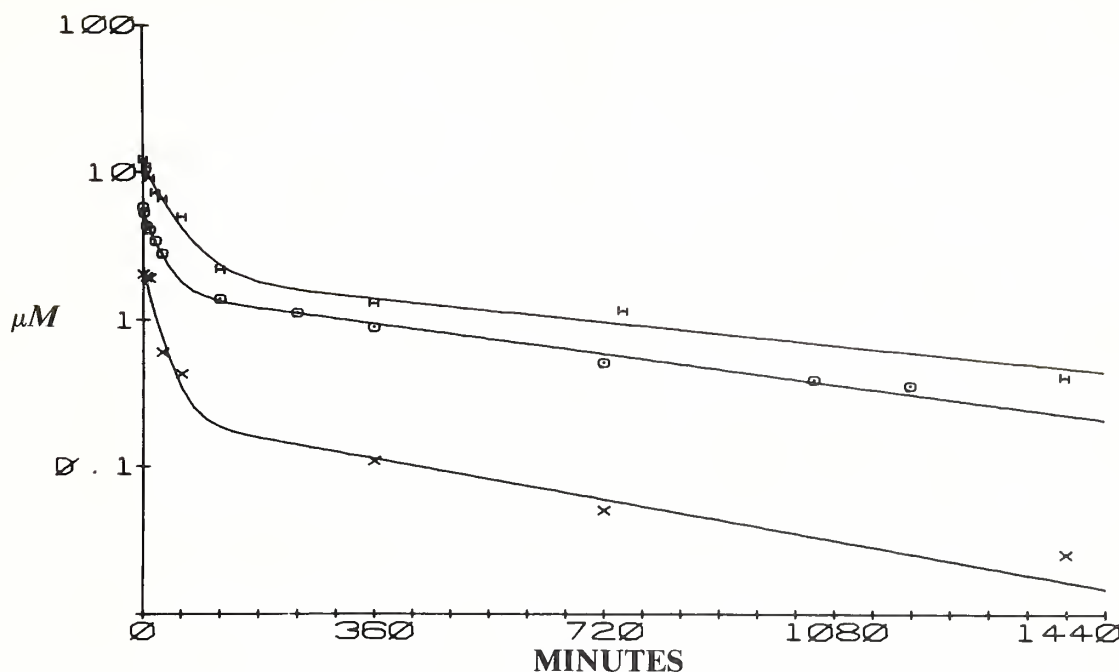


Fig. 1. Typical biphasic plasma disappearance curves for patients treated with Taxol at 60 mg/m² (x), 170 mg/m² (o), and 265 mg/m² in a phase I study of Taxol administered as a 6-hour infusion (20). Time 0 represents the time at the end of the infusion.

pharmacokinetic studies, which indicated that the pharmacokinetic behavior of Taxol is linear. Instead, the nonlinear or saturable pharmacokinetic behavior of drugs that truly behave in a nonlinear fashion usually becomes evident when shorter administration schedules are used. When such agents are administered over long durations, plasma concentrations are generally low, often significantly lower than K_m , the Michaelis-Menten constant; elimination and/or tissue distribution processes are not saturated; and pharmacokinetics appear linear or first-order. However, nonlinear or zero-order kinetics become apparent when the identical agents are administered over shorter durations, resulting in higher plasma concentrations that approach or exceed K_m . At higher plasma concentrations, elimination and/or tissue distribution processes are relatively saturated. Although a nonlinear pharmacokinetic profile may be due to saturable elimination and/or tissue distribution processes, the disproportionate increases in C_{max} , as well as AUC, with increasing doses of Taxol indicate that the principal saturable process occurs during drug elimination; however, Taxol's nonlinear behavior may also be due, in part, to saturable tissue distribution (29,32). Taxol's nonlinear pharmacokinetic profile may have several important clinical implications. First, it is possible that dose escalations, especially on shorter (e.g., 3-hour) administration schedules, will result in disproportionate increases in both AUC and C_{max} along with a disproportionate increase in toxicity. Similarly, dose de-escalations may result in disproportionate decreases in AUC and/or C_{max} , potentially decreasing antitumor activity. Therefore, it will be important to

clearly define these nonlinear pharmacokinetic and pharmacodynamic relationships in the future.

Mean central (VD_c) and steady state (VD_{ss}) volumes of distribution generally have been large, with mean VD_c ranging from 8.6 to 19.2 L/m² (cumulative mean, 13.8 L/m²) and mean VD_{ss} ranging from 48.2 to 182.0 L/m² (cumulative mean, 87 L/m²). These values are substantially larger than the volume of total body water, indicating that Taxol is extensively bound to plasma proteins and/or other tissue elements, possibly tubulin. Indeed, the magnitude of binding of Taxol to plasma proteins, as determined by both ultrafiltration and equilibrium dialysis, has ranged from 95% to more than 97% over a wide range of drug concentrations (15-17,18). However, Taxol is readily eliminated from the plasma compartment despite extensive plasma protein binding, a finding that is consistent with limited preclinical data (14) and suggests lower affinity and reversible binding.

Limited data are available pertaining to the tissue distribution of Taxol in humans and other species. These limited studies indicate that Taxol distributes into some third space fluid collections (e.g., pleural fluid, ascites). For example, biologically relevant Taxol concentrations (>0.1 μmol/L) were detected in the ascites of one patient 7 hours after drug administration (16). Taxol concentrations in the ascitic fluid progressively increased for several hours thereafter, reaching a maximum concentration that was approximately 40% above levels achieved concurrently in plasma. Additionally, levels of this magnitude persisted for at least 12 hours. In contrast, Taxol was not detected

in the cerebrospinal fluid of leukemia patients receiving doses ranging from 250 to 390 mg/m² (21).

The preliminary results of tissue distribution studies using radiolabeled Taxol in animals have been reported (35,36). Lesser et al. sampled tissues 2 hours after the administration of ³H-Taxol to rats (35). Following whole-tissue extraction and autoradiography, tissue:plasma ratios were high in almost all tissues sampled, including liver (90:1), heart (80:1), lung (77:1), muscle (23:1), and spleen (89:1). Ratios were particularly high in tissues that are involved in organ barrier filtration, including the portal triad (323:1), renal medulla (263:1), choroid plexus (105:1), and glomeruli (259:1). Lesser et al. and Klecker et al. detected either no penetration or very limited penetration of the radioisotope into the testes and the brain, which are generally considered "tumor sanctuary" sites (35,36). Eiseman et al. determined that blood/brain and blood/testes partition coefficients are 0.010 and 0.14, respectively, whereas liver partition coefficients were much greater, 5.24 and 4.07 in male and female mice, respectively (37). In addition, although peripheral neurotoxicity is a principal dose-limiting nonhematologic effect of Taxol, radioactivity has not been detected in the peripheral nervous system following the administration of ³H-Taxol to rats (35).

RELATING PHARMACOLOGIC PARAMETERS TO DRUG ACTIVITY

C_{\max} values achieved with Taxol given at recommended phase II doses have ranged from 2.54 to 12.5 $\mu\text{mol/L}$ with 3-hour infusions (135 to 300 mg/m²); 3.1 to 4.1 $\mu\text{mol/L}$ with 6-hour infusions (210 to 250 mg/m²); 0.72 to 0.94 $\mu\text{mol/L}$ with 24-hour infusions (200 to 250 mg/m²); and 0.053 to 0.077 $\mu\text{mol/L}$ with the 96-hour infusion schedule (120 to 160 mg/m²) (15-23,29,30,32-34,38,39). Using the mean kinetic parameter values for drug disposition and elimination derived from early phase I and pharmacokinetic studies at the Johns Hopkins Oncology Center (JHOC) (20), plasma Taxol concentrations achieved at the end of 24-hour infusions (C_{\max}) have been calculated to be nearly equal, on average, to the steady-state values (C_{ss}) ($C_{24-h} = 0.97 C_{ss}$) (22). All Taxol C_{\max} values achieved with infusion durations ranging from 3 to 24 hours and C_{ss} values achieved with 24-hour infusion schedules have been several orders of magnitude higher than drug concentrations (0.01 to 0.1 $\mu\text{mol/L}$) that have consistently been demonstrated to induce cytotoxicity, as well as pertinent biological and antimicrotubule effects (e.g., microtubule bundle formation) in vitro (40-43). However, direct comparisons made between Taxol concentrations in vitro and those achieved in vivo may not be entirely valid due to differences in protein concentrations and, therefore, to differences between protein bound and unbound fractions, though the binding of Taxol to plasma proteins appears to be of low affinity and reversible. (See "Pharmacokinetics" section.)

TAXOL RESISTANCE

In studies using human leukemia cell lines in vitro, clinically relevant concentrations of Taxol (0.1 to 10 $\mu\text{mol/L}$) have been demonstrated to induce at least two distinct morphological effects on microtubules as assessed by both electron microscopy and indirect immunofluorescence staining (40-42). First, Taxol-treated cells form abundant arrays of disorganized microtubules that are often aligned in parallel bundles. Taxol induces the formation of abnormal microtubule bundles in cells during all phases of the cell cycle. In addition, Taxol induces the formation of large numbers of abnormal spindle asters during mitosis. These Taxol-treated mitotic cells form excessive numbers of abnormal asters that do not require centrioles for enucleation and are reversible following treatment. Although the precise mechanisms that account for inherent resistance to Taxol have not been clearly defined, several interesting observations have been made. First, the sensitivity of these cell lines to the cytotoxic effects of Taxol is directly related to the sensitivity of the cells to form irreversible microtubule bundles. Second, whereas sensitive cell lines primarily form irreversible bundles and are critically affected during interphase, most relatively resistant cells are unaffected during traverse through G₀/G₁ and S phases and accumulate in G₂/M with subsequent formation of multiple abnormal asters. Finally, most resistant cells that form asters also contain polyploid DNA content after prolonged drug exposure and the magnitude of DNA polyploidization appears to be related to drug resistance. In a phase I trial of Taxol in leukemia, the sensitivity of leukemic blasts to form microtubule bundles ex vivo (Fig. 2) was directly related to the magnitude of clinical antitumor activity (Table 2) (21). These results suggest that microtubule bundles and DNA polyploidization may be useful indices of lethal drug effects, indices that could be performed on clinical material and evaluated prospectively in clinical trials.

Two mechanisms of acquired resistance to Taxol have also been well characterized to date. Both mechanisms are described extensively elsewhere in this monograph. One mechanism of acquired Taxol resistance involves the development of altered α - and β -tubulin proteins, which confer an impaired ability to polymerize tubulin dimers to form microtubules (44). These cells lack normal microtubules in their interpolar mitotic spindles when grown in the absence of Taxol; the continuous presence of Taxol is required for microtubule assembly to proceed normally. These mutants appear to compensate for the continuous presence of Taxol by slowing their intrinsic rate of microtubule assembly. A second mechanism of acquired Taxol resistance is conferred by the multidrug-resistant (MDR) phenotype that involves the amplification of membrane p-glycoproteins that function as drug efflux pumps (45-49). The MDR genotype confers varying degrees of cross-resistance to many classes of structurally bulky, natural products, including the vinca alkaloids, Taxol, Taxotere², colchicine, doxorubicin, and etoposide. Another notable feature of MDR is that resis-

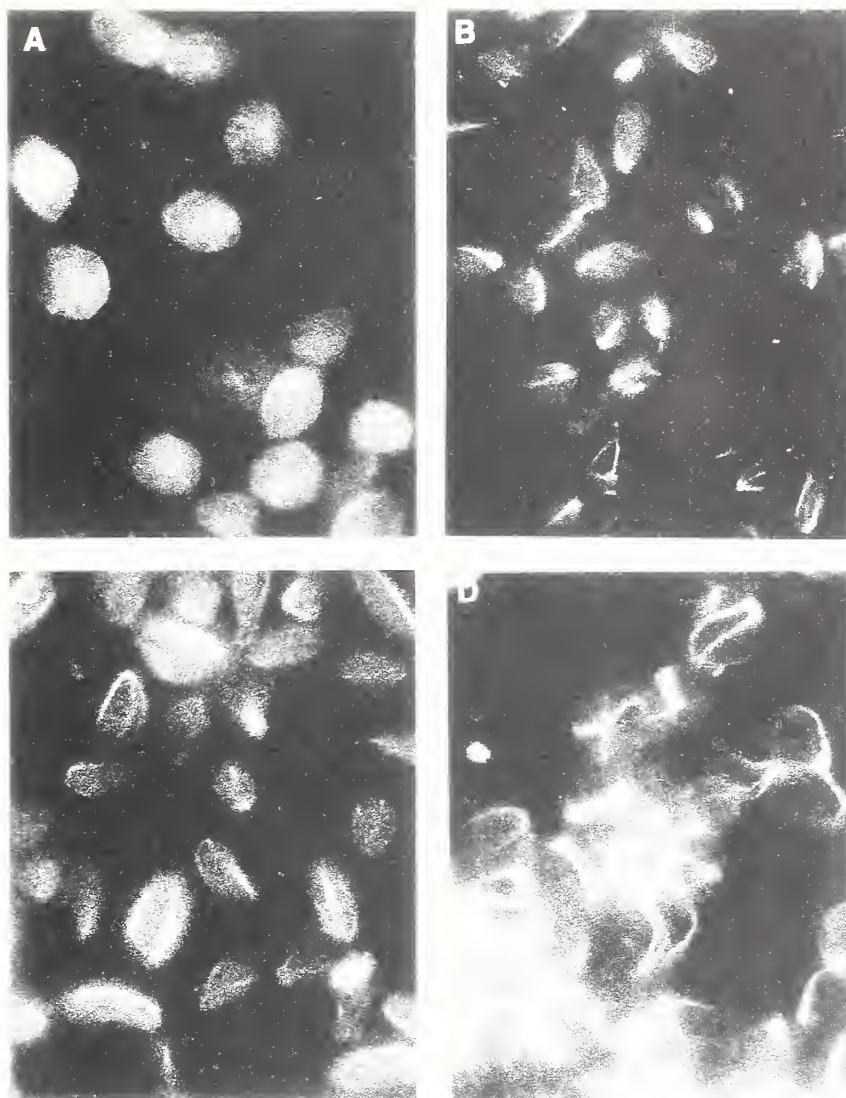


Fig. 2. Indirect immunofluorescence staining of tubulin following incubation of patient's blasts with Taxol pretreatment (21). A, Blasts of patient 14, untreated; B, Blasts of patient 17 following ex vivo treatment with 10 μ M Taxol for 22 h; C, Blasts of patient 16 following ex vivo treatment with 1.0 μ M Taxol for 22 h; and D, Blasts of patient 3 following ex vivo treatment with 1.0 μ M Taxol for 22 h.

tance to many agents, including the taxanes, can be reversed by diverse classes of drugs, such as calcium channel blockers, tamoxifen, cyclosporin A, and some antiarrhythmic agents (45-49). However, the clinical relevance of both mechanisms of acquired drug resistance is not clear at this time. Clinical trials of Taxol combined with modulators of MDR, specifically cyclosporin A and verapamil, are currently ongoing at Stanford University Medical Center and NCI.

RELATING PHARMACOLOGIC PARAMETERS TO TOXICITY

A limited number of early phase I studies sought to identify relationships between Taxol-induced toxicities and pertinent pharmacologic parameters. The severity of

leukopenia was found to correlate roughly with Taxol AUC during early phase I trials in which Taxol was administered on 6-hour infusion schedules at JHOC and the University of Texas, San Antonio (UTSA) (15,20). A more recent analysis of the JHOC trial data revealed, however, that the relationship between the percentage decrease in the white blood cell (WBC) count, Taxol's principal toxicity, and AUC is much better characterized by a sigmoidal maximal effect (E_{max}) model, which is generally a more appropriate model for describing saturable biological processes compared with linear models as used in the previous analyses (Rowinsky EK: unpublished data). The percentage change in the WBC counts was related to AUC by the following formula:

$$\% \text{ change in WBC} = 100 \times \text{AUC}^{1.04} / (1372 + \text{AUC}^{1.04}).$$

Table 2. In vitro sensitivity of leukemic blasts to Taxol-induced microtubule bundles

Patient no.	Diagnosis (FAB*)	Taxol dose (mg/m ²) (peak Taxol concentration μ M)	Response [†]	Microtubule bundles produced ex vivo [‡]
6	ANLL (M5)	250 (1.19)	Stable	—
11	ANLL (M4)	250 (1.21)	Stable	—
		315 (5.49)		
4	ANLL (M2)	250 (2.06)	Progression	—
7	ANLL (M4)	315 (1.95)	Progression	—
		390 (2.54)		
15	ANLL (M4)	315 (4.75)	Decrease in blasts	+
		315 (2.38)		
12	ANLL (M2)	390 (4.25)	Complete clearance	+++
16	ANLL (M7)	315 (2.58)	Decrease in blasts	++
14	ANLL (M4)	390 (9.45)	Decrease in blasts	++
		315 (2.38)		
9	Biphen	315 (0.63)	Decrease in blasts	+
		390 (1.20)		
17	Biphen (Ph ¹)	315 (2.74)	Decrease in blasts	+++
3	ALL (L3)	200 —	Complete clearance	+++
		250 (2.18)		
		315 (5.16)		
13	ALL (L2)	390 (0.79)	Complete clearance	++
		390 (2.77)		

*French-American-British classification of leukemia.

[†]Response: stable, no change in numbers of blasts; progression, increase in numbers of blasts; complete clearance, temporary complete clearance of peripheral blood and bone marrow blasts; decrease in blasts, decrease but less than complete clearance of bone marrow and peripheral blood clearance.

[‡]Bundles produced ex vivo: —, no bundles; +, $\geq 20\%$ of cells with bundles after 10μ M Taxol \times 4–22 h; ++, $\geq 20\%$ of cells with bundles after 1–10 μ M Taxol \times 4–22 h; and +++, $\leq 20\%$ of cells with bundles after 0.1–10 μ M Taxol \times 4–22 h.

This relationship is depicted in Fig. 3. Similarly, the percentage change in ANC in untreated and minimally pretreated patients receiving Taxol 135 to 350 mg/m² (24-hour infusion) before cisplatin 75 to 100 mg/m² and granulocyte-colony stimulating factor (G-CSF) has also been well characterized by an E_{\max} model (23). The percentage change in the ANC was related to Taxol C_{ss} by the following formula:

$$\% \text{ change in ANC} = 100 \times C_{ss} / (0.36 + C_{ss}).$$

Preliminary data from the NCIC-European Ov. 9 trial, in which previously treated patients with ovarian cancer were randomized to treatment with Taxol given over 24 or 3 hours and then randomized to treatment with either 135 mg/m² or 175 mg/m², have indicated that both AUCs and C_{\max} values are substantially higher when identical doses of Taxol are administered over 3 hours compared with 24 hours, but neutropenia was more severe in patients receiving Taxol over 24-hours (30,31). Further, the severity of neutropenia was related to neither AUC, clearance, nor C_{\max} . Instead, the percentage decreases in both the WBC and the ANC have been well characterized by an E_{\max} model that relates these parameters to the duration that plasma Taxol concentrations are maintained above 0.1 μ mol/L.

Neurotoxicity grade was also demonstrated to roughly correlate with AUC in an early phase I study at UTSA (19). In this study, the grade of neurotoxicity also roughly

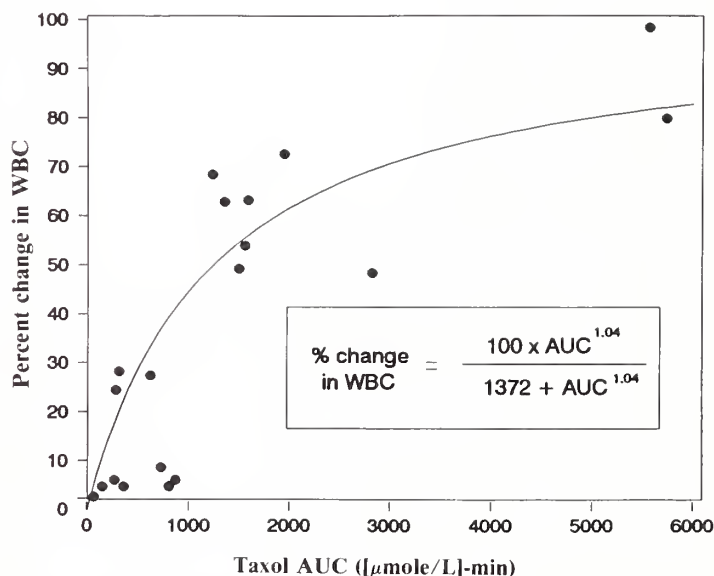


Fig. 3. The percentage decrease in WBC versus AUC during course 1 for patients treated with Taxol administered as a 6-hour infusion (20). The curve is fit to a sigmoidal E_{\max} model.

correlates with AUC using a linear model (15). Similarly, neurotoxicity roughly correlated ($r = 0.54$, $P < .01$) with Taxol C_{ss} in a phase I trial of Taxol (135 to 350 mg/m²) combined with cisplatin (75 to 100 mg/m²) and G-CSF

at JHOC. However, the correlation between the grade of neurotoxicity and Taxol dose was nearly identical ($r = 0.56$, $P < .01$), indicating that Taxol dose may be equivalent to Taxol C_{ss} in predicting for the development of neurotoxicity (23); see article on the neurotoxicity of Taxol in this monograph.

Additionally, a significant relationship between Taxol C_{ss} and mucositis was noted in a study of Taxol administered as a 96-hour continuous infusion at NCI (38,39). Patients with $C_{ss} \geq 0.07 \mu M$ developed grade 2 or 3 mucositis, whereas significant mucositis occurred in none of seven patients with $C_{ss} < 0.07 \mu mol/L$. These investigators also demonstrated that the extent of liver involvement with metastatic breast cancer was directly related to Taxol C_{ss} and, therefore, indirectly related to Taxol clearance. Similar relationships between toxicities and pertinent pharmacologic parameters are also being sought in ongoing prospectively randomized Eastern Cooperative Oncology Group (ECOG) and Gynecologic Oncology Group (GOG) studies of Taxol.

DRUG DISPOSITION

The systemic clearance of Taxol ranged from 100 to 933 mL/min/m² (cumulative mean, 496 mg/min/m²) in phase I single-agent trials; however, the principal mechanism of systemic clearance was not defined during early pharmacologic studies. Mean values for urinary excretion ranged from 1.4% to 8.2% (cumulative mean, 5.5%) (Table 1), indicating that renal clearance contributes minimally to systemic clearance. This suggests that metabolism, biliary excretion, and/or extensive tissue binding are responsible for the bulk of the agent's systemic clearance. Additionally, metabolites were identified in neither plasma nor urine in early phase I studies, except for a new peak that eluted before Taxol, which was detected in the plasma of a single patient by reverse-phase HPLC (50). The peak was not felt to be due to 7-epitaxol because this epimer elutes after Taxol. Therefore, it was assumed that the peak was due to a new, and as yet unidentified, metabolite. Spontaneous conversion of Taxol to 7-epitaxol was demonstrated to occur in normal saline solution at 37°C after 48 hours as well as in tissue culture medium (15,51). Approximately 50% of Taxol was demonstrated to convert to 7-epitaxol in the culture medium of the J774.2 murine macrophage cell line after 72 hours of drug treatment (51). The conversion was reversible, however, and 7-epitaxol was also partially converted to Taxol under the same conditions. However, using a highly sensitive HPLC assay, Huizing et al. recently reported on the detection of several new possible metabolite peaks in the end of infusion plasma of patients receiving 3-hour infusions of Taxol (25). However, the structures of these metabolites have not been identified to date.

High concentrations of Taxol and hydroxylated metabolites have been identified in both rat and human bile (52-55). An extensive description of the methods and results of these studies are discussed by Monsarrat et al. in

this monograph (55). Briefly, Monsarrat et al. initially reported that the disposition of only 10% of a dose of Taxol administered to rats could be accounted for by renal excretion. Neither plasma nor urinary metabolites were detected. Approximately 40% of an administered dose of Taxol in rats was recovered, however, as both parent compound and metabolites from bile collected for 24 hours after treatment. Similarly, approximately 20% of the dose of Taxol administered to a patient with a biliary drainage catheter was recovered as both parent compound and metabolites from bile collected for 24 hours following treatment. Monsarrat and coworkers subsequently reported on the detection and identification of several metabolites in both human and rat bile using analytical HPLC, mass spectrometry, and NMR spectroscopy (52-55). Neither glucuronodated nor sulfated metabolites were identified; however, nine and five metabolite peaks were detected in rat and human bile, respectively. To date, all human metabolites identified have intact side chains at positions C-2 and C-13 of the taxane ring. Baccatin III, however, which lacks the side chain at position C-13 of the taxane ring, was identified as a minor metabolite in rats only. With the exception of baccatin III, all biliary metabolites identified thus far are hydroxylated derivatives. To date, Monsarrat et al. have identified three of the nine metabolites in rat bile as monohydroxylated and one metabolite as dihydroxylated. Similarly, among the four metabolites detected in human bile, two have been identified as monohydroxylated derivatives, and one has been identified as a dihydroxylated derivative. Interestingly, the major metabolite of Taxol in human bile, a monohydroxylated derivative with a single hydroxyl group on position C-6 of the taxane ring, was not identified in rat bile, whereas the major metabolite in rat bile, a monohydroxylated metabolite with a single hydroxylated group on the side chain at position C-13, was only a minor metabolite in human bile. The hydroxylated nature of these metabolites suggests that P-450 mixed function oxidases play a major role in metabolizing Taxol, but interspecies differences in the sites of hydroxylation also suggest that different P-450 enzyme isoforms may be involved.

Although high concentrations of Taxol and several metabolites have been identified in rat and human bile, the majority of drug disposition has not been accounted for. It is possible that other, as of yet unidentified, metabolites are similarly metabolized and excreted into bile; however, the previous studies did not assess biliary for periods exceeding 24 hours posttreatment. Recently, Gaver et al. reported on the recovery of 98% of radioactivity in rat feces collected for 6 days following the administration of ¹⁴C-Taxol, while <10% of radioactivity was recovered from urine (56).

INTRAPERITONEAL PHARMACOKINETICS

In addition to impressive activity in advanced and platinum-resistant ovarian cancers, Taxol possesses sev-

eral pharmacologic characteristics, including a high molecular weight, bulky chemical structure, and hepatic metabolism, which make it an attractive agent for intraperitoneal (IP) administration, especially in ovarian cancer, which is commonly confined to the peritoneal cavity, even in advanced stages. The induction of pertinent microtubule and cytotoxic effects in vitro also appears to be dependent on both concentration and exposure duration, factors that may be optimized by regional drug delivery. To date, the feasibility of IP administration using single doses of Taxol (25 to 200 mg/m²) has been studied (57). Severe abdominal pain, which occurred above Taxol doses of 125 mg/m², was dose-limiting. Systemic toxicities were mild at doses less than 175 mg/m².

Pharmacologically, the study demonstrated that Taxol may be an ideal drug for IP use. The correlation between administered IP dose and peak IP concentration, as well as the low apparent V_D that resulted (mean \pm , 1.9 ± 0.3 L/m²; range 0.5 to 5.0 L/m²), suggested that initial drug distribution is principally confined to the peritoneal cavity. Peak IP Taxol concentrations ranged from 19 to 324 μ mol/L at doses of 25 to 175 mg/m². These peak concentrations, including peak concentrations at the recommended phase II dose, 125 mg/m² (mean, 198 μ mol/L), were several orders of magnitude higher than levels required to induce pertinent microtubule and cytotoxic effects in vitro (40–43). Taxol concentrations of this magnitude were maintained for several days, indicating that IP clearance is extremely slow. In fact, the mean clearance of Taxol from the peritoneal cavity was calculated to be 0.42 ± 0.09 L/m²/day (range, 0.13 to 0.91 L/m²/day). In addition, although protein-binding studies were not performed, the low levels of protein in the infusate infers that the majority of drug is unbound compared with Taxol in plasma. A representative IP elimination curve is depicted in Fig. 4. Peak plasma levels were typically achieved by 1 hour and ranged from <0.05 μ mol/L (lower limits of detection) to 0.86 μ mol/L, but mean peak plasma concentrations correlated roughly with administered dose ($r = 0.66$, $P > .2$). Additionally, these concentrations generally exceeded minimal concentrations required to induce pertinent effects in vitro and are encouraging because the achievement of relevant systemic concentrations may be an important criterion for drugs to meet to be efficacious when given by the IP route. Furthermore, a profound IP exposure advantage for Taxol was demonstrated, with IP/systemic AUC ratios ranging from 336 to 2890 times (mean \pm SE, 996 ± 93). Given the dose-limiting toxicity, as well as the extremely high Taxol concentrations and AUCs achieved with this schedule, the administration of lower IP doses on a weekly schedule is currently being studied by the GOG. Thus far, weekly doses up to 60 mg/m² have been well tolerated with minimal abdominal pain and systemic toxicity (58). The preliminary results of complementary pharmacologic studies also demonstrated the achievement of IP Taxol levels >100 μ mol/L in all patients, with a similar magnitude of high concentrations persisting at 72 to 120 hours in some patients.

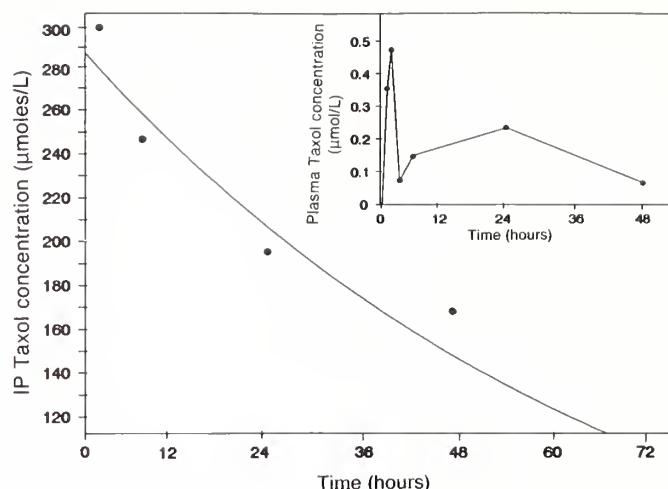


Fig. 4. IP Taxol disposition curve for patient treated with 175 mg/m² of Taxol administered IP. Inset: plasma concentration over the same time period (57).

COMBINATION CHEMOTHERAPY: SEQUENCE-DEPENDENT DRUG INTERACTIONS

The potential for pharmacologic interactions between Taxol and other antineoplastic agents is well illustrated by the results with the Taxol–cisplatin drug combination. In a phase I study of Taxol and cisplatin at JHOC, minimally pretreated patients received alternating sequences of both agents to determine if drug sequencing influenced the toxicity patterns and pharmacologic behavior of either agent (22). Despite the overlapping neurotoxicity of these agents, mild to modest neurotoxicity occurred in only 27% of patients receiving interactions of Taxol at doses ranging from 110 to 200 mg/m² and cisplatin at doses ranging from 50 to 75 mg/m². Instead, neutropenia was dose-limiting. Mean absolute neutrophil count (ANC) nadirs were significantly lower and the percentage of courses associated with ANCs $\leq 500/\mu$ L was significantly higher when patients received cisplatin before Taxol. To determine if drug sequencing affected the pharmacologic disposition of Taxol, clearance rates for Taxol were calculated during courses in which Taxol was given before cisplatin ($Cl_{t/c}$) and courses in which cisplatin was given before Taxol ($Cl_{c/t}$). Paired Taxol clearance data for 15 individuals are depicted in Fig. 5. Overall, mean Taxol clearance rates were lower when Taxol followed cisplatin, 321 ± 44 mL/min/m² (range, 99 to 844 mL/min/m²) compared with 405 ± 65 mL/min/m² (range, 141 to 1097 mL/min/m²) for the alternate sequence, Taxol followed by cisplatin ($P = .013$ by paired *t*-test). Correlation analysis of the paired clearance data revealed a linear relationship ($r = 0.93$, $P < .001$), and regression analysis demonstrated that the clearance rate values for alternate sequences were defined by the following relationship:

$$Cl_{c/t} = 0.75 Cl_{t/c}$$

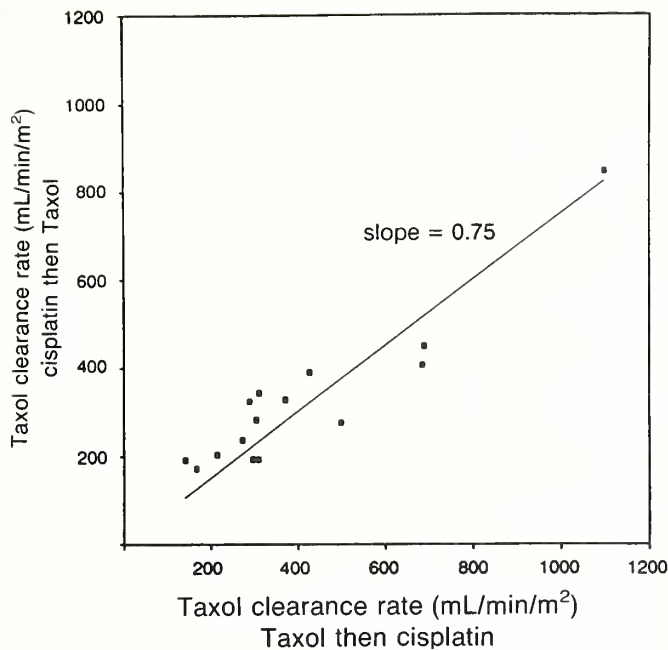


Fig. 5. Taxol clearance rates in 18 individual patients measured when cisplatin precedes Taxol and when Taxol precedes cisplatin. Relationship is linear ($r = 0.93$, $P < .001$) with a slope of 0.75 (22).

Although the mechanism for sequence-dependent interactions between Taxol and cisplatin is not known, one potential mechanism is the inhibition of possible cytochrome P-450-dependent Taxol-metabolizing enzymes by cisplatin (see "Drug Disposition" section) because some platinum compounds, including cisplatin but not carboplatin, have been demonstrated to modulate specific cytochrome P-450 enzymes (59).

Not only did the sequence of cisplatin followed by Taxol induce more profound myelosuppression, but it was also demonstrated to be the suboptimal sequence with respect to cytotoxicity activity against L1210 leukemia in concurrent compared with the reverse sequence as well as simultaneous drug treatment (60). In contrast, the sequence of Taxol followed by cisplatin, which was associated with less neutropenia *in vivo*, was the sequence that produced maximal cytotoxicity against L1210 leukemia cells. Therefore, Taxol followed by cisplatin appeared to be a logical selection for the experimental treatment arm for subsequent phase II/III trials, including a multicenter GOG randomized phase III study of Taxol and cisplatin versus cyclophosphamide and cisplatin in untreated patients with suboptimally debulked ovarian epithelial neoplasms, as well as in additional studies of higher doses of Taxol combined with cisplatin and G-CSF at JHOC and ECOG.

The potential for sequence-dependent interactions has also been studied in conjunction with developmental studies of Taxol-doxorubicin drug combinations for breast cancer. In the first study of the Taxol-doxorubicin doublet at the University of Texas M. D. Anderson Cancer Center, Holmes et al. reported that severe stomatitis was

dose-limiting at the first dose level when Taxol (125 mg/m² as a 24-hour infusion on day 1) preceded doxorubicin (60 mg/m² as a 48-hour infusion on days 2 and 3) and G-CSF (5 µg/kg/day, days 4–9) (61,62). The maximum tolerated doses were Taxol 125 mg/m² and doxorubicin 48 mg/m²; however, a substantial proportion of patients required dose reductions during subsequent courses. To evaluate the effects of drug sequencing on toxicity, these investigators initiated a second phase I trial in which sequencing was reversed. In this study, doxorubicin was administered on days 1 and 2 (48-hour infusion) and Taxol (24-hour infusion) was begun on day 3, followed by G-CSF (5 µg/kg/day on days 4–9). The latter sequence has been much better tolerated, and dose escalation has safely proceeded to Taxol 150 mg/m² and doxorubicin 60 mg/m². Similar results were also noted during pilot studies of Taxol and doxorubicin, in which doxorubicin was administered on a standard bolus schedule. Similar to the M. D. Anderson studies, mucositis occurred only in patients receiving Taxol before doxorubicin compared with the reverse sequence of drugs administered at identical doses (Sledge G: personal communication). Based on these data, the ECOG is currently utilizing the sequence of doxorubicin (bolus) before Taxol (24-hour schedule) in phase III clinical trials in which patients with untreated metastatic breast cancer are randomized between treatment with doxorubicin alone, Taxol alone, and the Taxol-doxorubicin doublet.

PHARMACOLOGY IN PATIENTS WITH ALTERED PHYSIOLOGY

Because patients with abnormal renal and hepatic excretory functions were not eligible to participate in early phase I, II, and III studies of Taxol, only limited information is available pertaining to the pharmacologic behavior and toxicity of Taxol in patients with abnormal excretory organ function. As discussed previously, the renal excretion of Taxol has been consistently demonstrated to be negligible (mean, 5.5%), and urinary metabolites have not been identified to date. This suggests that dose modifications may not be necessary for patients with mild to moderate renal dysfunction. However, the magnitude of excretion of both Taxol and metabolites into bile in humans and rats is similar to that of other anticancer agents, such as the vinca alkaloids, in which dose modifications are required for hepatic excretory dysfunction. As previously discussed, it is also possible that other, as of yet unidentified, metabolites are similarly excreted into bile. For these reasons, phase I and pharmacologic studies of Taxol in patients with excretory organ dysfunction are ongoing. The Cancer and Leukemia Group B is currently conducting one such phase I and pharmacologic study of patients with hepatic dysfunction. A retrospective analysis in 358 patients with and without mild elevations in liver function tests (predominantly elevations in hepatocellular enzymes because study eligibility was restricted to patients with elevated plasma levels of total bilirubin) or mild decreases

in renal function participating in early phase II trials revealed no differences in the severity of both hematologic and nonhematologic toxicities in these abnormal groups (Bristol-Myers Squibb: unpublished data on file). In contrast, Wilson et al. reported that patients with abnormal liver-function tests ($\text{ALT} > 2 \times \text{normal}$) had significantly reduced Taxol clearance rates in a phase I study of Taxol administered as a continuous 96-hour infusion (38,39). Ten patients with normal ALT had a mean Taxol clearance of 496 ± 77.7 , and two patients with an elevated ALT had a mean Taxol clearance of 266 ± 38.2 , significantly higher Taxol C_{ss} , and more severe mucositis requiring dose reductions. In addition, the severity of both hematologic and nonhematologic toxicities does not appear to be affected by age. Elderly patients (age > 65 years) who participated in early phase II studies developed similar myelosuppressive and nonhematologic effects compared with younger patients (Bristol-Myers Squibb: unpublished data on file). The pharmacologic disposition of Taxol in elderly patients has not been systematically evaluated, however.

FUTURE DIRECTIONS

Although several biliary metabolites have been identified, the pharmacologic disposition of the bulk of an administered dose of Taxol has not yet been determined. One possibility is that a substantial proportion is not metabolized and avidly binds to tubulin and/or other proteins for relatively long durations. A study involving the JHOC, Research Triangle Institute, NCI, and Bristol-Myers Squibb is being planned to determine the complete metabolic fate of Taxol using ^{14}C -labeled drug. Metabolic studies are also important supplements to other clinical trials that will focus on establishing criteria for the optimal dosing of Taxol in patients with excretory organ dysfunction and trials that will evaluate the optimal use of Taxol in combination with other antineoplastic agents and assess potential interactions with other unrelated classes of agents.

Even though the extent of hepatic metabolism may be low overall, it may still be significant enough to account for substantial interactions between Taxol and other classes of antineoplastic agents, particularly agents that may modulate or be metabolized by cytochrome P-450 enzymes. Although the mechanism for sequence-dependent interactions between Taxol and cisplatin are unknown, similar interactions may occur when Taxol is combined with other antineoplastic agents that either differentially inhibit P-450 enzyme functions or are metabolized, in part, by P-450 enzymes (e.g., anthracyclines). The steps taken to develop the Taxol-cisplatin doublet, which involved an extensive evaluation of toxicologic and pharmacologic differences between drug sequences during phase I testing and the effects of drug sequencing on cytotoxicity *in vitro*, could be used as a model to develop other Taxol-based drug combinations. These types of studies are currently being incorporated into developmen-

tal studies of Taxol combined with cyclophosphamide, topotecan, and doxorubicin at JHOC.

Another potential source of drug interactions and variable clinical results may be due to the differential effects of H_2 -histamine antagonist premedications on the hepatic metabolism of Taxol. H_2 -histamine antagonists have been used successfully for prophylaxis against hypersensitivity reactions (reviewed in 13,63). Although cimetidine has been the most commonly administered H_2 -antagonist in clinical trials to date, ranitidine and famotidine have also been used, and the availability of these agents often differs significantly among practitioners. H_2 -histamine antagonists have variable modulatory effects on the activities of many hepatic P-450 enzymes, which may be involved in critical steps in the metabolism of Taxol (64,65). Therefore, the use of different H_2 -histamine antagonists in clinical trials may portend variable effects on drug metabolism and may differentially affect antitumor activity and toxicity patterns. Both animal and human studies are underway to assess this potentially important pharmacologic concern. Preliminary results of an ongoing study at JHOC in which patients participating in the NCI Treatment Referral Center ovarian cancer study are being randomized to receive either famotidine 20 mg IV or cimetidine 300 mg IV before one course of Taxol and then crossed over to the alternate H_2 -histamine antagonist before the next course is currently available (66). To date, this study has failed to demonstrate substantial pharmacologic and toxicologic differences (66; Slichenmyer W and Rowinsky E: unpublished data). In addition, cimetidine has not been demonstrated to alter either the metabolism and biliary excretion of ^3H -Taxol in rats or the metabolism of ^3H -Taxol in microsomal preparations *in vitro* (36,67). With respect to the effects of other microsomal inhibitors on the metabolism of ^3H -Taxol *in vitro*, both ketoconazole and fluconazole, but not erythromycin, have been demonstrated to be inhibitory (67). It is clear that a concerted effort must be made to study the potential for antineoplastic agents and other commonly administered agents to modulate the pharmacologic behavior of Taxol.

The simultaneous initiation of phase II and III trials in multiple tumor types involving hundreds of patients will also be a unique opportunity to study population pharmacokinetics, and more importantly, population pharmacodynamics, particularly with respect to the influence of critical pharmacologic indices, such as steady-state concentrations and AUC, on response and toxicity. Several randomized phase II and III trials, which will evaluate different Taxol doses and schedules, will incorporate limited pharmacologic studies prospectively to address these pharmacodynamic questions.

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²Taxotere is used in this monograph to refer to the drug that now has the generic name docetaxel and the registered trade name Taxotere® (Rhône-Poulenc-Rorer Pharmaceuticals Inc., Collegeville, Pa.).

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

Hepatic Metabolism and Biliary Excretion of Taxol in Rats and Humans

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To date there have been limited studies of the metabolism and disposition of Taxol in animals and humans. Renal disposition of unmetabolized Taxol has been documented to account for a maximum of 5% to 10% of an administered dose of Taxol in humans, but the principal processes involved in drug disposition, particularly the roles of biliary excretion and drug metabolism, have not been evaluated. Therefore, the biliary excretion of Taxol has been studied in rats and in a human patient receiving Taxol in a phase I trial. Of the total doses administered to rats and the patient, 40% and 20%, respectively, were excreted in the bile in the forms of unmetabolized Taxol and Taxol metabolites until 24 hours posttreatment. Although the biliary excretion of unmetabolized Taxol accounted for 10% and 3% of total drug disposition in the rats and in the patient, respectively, the remaining portion consisted of several metabolites. Nine metabolites were detected in rat bile, and five metabolites were detected in human bile. The chemical structures of four of the rat metabolites and three of the human metabolites have been identified thus far. With the exception of baccatin III, a minor metabolite found only in rat bile that lacks the side chain at C-13 position of the taxane ring, the other metabolites were monohydroxylated or dihydroxylated and had intact taxane rings and side chains at taxane ring positions C-2 and C-13. The taxane ring and both the C-2 and C-13 side chains were susceptible to hydroxylation. Although all major metabolites were hydroxylated, interspecies differences in the proportions of these metabolites in bile and the specific sites of hydroxylation were evident. In rats, the overall excretion of unmetabolized Taxol and metabolites 1) is not affected by pretreatment with various inducers of cytochrome P-450 enzymes which may be involved in the hydroxylation of Taxol, including benzopyrene, troleandomycine, or phenobarbital, but the percentage of minor metabolites increases after pretreatment with phenobarbital; 2) is higher in females than in males; and 3) increases in both sexes after pretreatment with cisplatin due to an enhanced clearance of unmetabolized Taxol [Monogr Natl Cancer Inst 15:39-46, 1993].

Although Taxol¹ is the prototypic drug of the taxane class of anticancer compounds and it possesses significant clinical anticancer activity in breast, ovarian, and lung cancers (1-9), its metabolism and disposition have not been well characterized to date. Pharmacologic studies

performed during phase I trials have demonstrated that renal elimination of unmetabolized Taxol accounts for a maximum of 5% to 10% of total drug disposition (*rev. in 10*), but the bulk of drug disposition has not been defined. In addition, human metabolites have not been identified.

Information pertaining to the metabolism of new chemotherapy agents, such as Taxol, may be extremely important for several reasons. First, this information may permit the formulation of recommendations for dose modifications in patients with abnormal excretory organ function. Second, the characterization of drug metabolism may allow clinicians to predict for the occurrence of deleterious drug interactions. For example, clinical and pharmacologic studies of sequences of Taxol and cisplatin have demonstrated that the principal toxicity, neutropenia, is greater when treatment with cisplatin precedes Taxol compared with the reverse sequence (11). Although pharmacologic interactions likely account for this sequence-dependent interaction because the clearance of Taxol is reduced by 25% when it is administered after cisplatin (11), the precise metabolic mechanism for these interactions is not known. Finally, the identification of active drug metabolites may result in the synthesis of more active analogues and attempts to modulate drug metabolism pharmacologically. Such attempts may be especially important for drugs, such as Taxol, that are in relatively limited supply.

The main features of Taxol metabolism in rats have been reported previously (12). This report describes the identification of additional metabolites and extends these analytic studies to a patient in which several metabolites have also been identified. In addition, the report details initial attempts to modulate the metabolism of Taxol and to explain the potential interactions between Taxol and cisplatin on a metabolic basis.

MATERIALS AND METHODS

Treatments of Rats

Bile was collected from 20 Sprague-Dawley rats that had been anesthetized with urethane (1 g/kg) given intramuscularly 2 hours before and 12 hours after cannulization of their biliary ducts. Taxol (10 mg/kg), which was

*See "Notes" section following "References."

formulated in 2 mL of a 1:1:8 mixture of polyethylene glycol hydroxystearate, dimethyl sulfoxide, and physiological saline, was then injected intravenously (IV) into the caudal vein. Bile samples were collected continuously during the 24 hours following the administration of Taxol. Timed-collections were obtained every 10 minutes for 1 hour after treatment, then hourly until 6 hours posttreatment, and finally every 6 hours until 24 hours posttreatment.

To evaluate the effects of various pharmacologic inducers of cytochrome P-450 enzymes, three male rats were treated with each of the following agents: benzopyrene (100 mg/kg), solubilized in oil, given intraperitoneally (IP) 2 days before Taxol (10 mg/kg, IV); phenobarbital (80 mg/kg), solubilized in 0.9% saline, given IP daily for 3 consecutive days before Taxol (10 mg/kg, IV); and troleandomycine (500 mg/kg, solubilized in oil) (13), given IP daily for 4 consecutive days before Taxol (10 mg/kg, IV). In addition, three control male rats received Taxol (10 mg/kg, IV), alone. To evaluate the effects of cisplatin on the excretion of biliary metabolites, cisplatin (7.2 mg/kg, in 0.9% saline) was administered IV to three male and three female rats 7 days before treatment with Taxol (10 mg/kg, IV). Taxol (10 mg/kg, IV) alone was also given to three male and three female rat controls.

Treatment of the Patient

Bile was obtained from a 63-year-old male with an extensive cholangiocarcinoma. The patient participated in a National Cancer Institute (NCI)-sponsored phase I and pharmacologic study of Taxol and cisplatin at the Johns Hopkins Oncology Center (Baltimore, Md.). Bile was collected continuously from a percutaneous catheter that was inserted after the patient was documented to have complete biliary obstruction. At the time of Taxol treatment, the patient's alkaline phosphatase was stable, albeit elevated in the range of 500–900 IU/L, and plasma concentrations of total and direct bilirubin, aspartate aminotransferase (SGOT), and alanine aminotransferase (SGPT) were within normal limits. Taxol (135 mg/m²) was administered as a continuous IV infusion over 24 hours. Further details pertaining to Taxol administration and formulation during this study were published previously (11). The patient also received a standard premedication regimen before Taxol, which consisted of dexamethasone, ranitidine, and diphenhydramine, for prophylaxis against major hypersensitivity reactions. Cisplatin (75 mg/m²) was administered as a 1 mg/min IV infusion following treatment with Taxol. Several antiemetic agents including dexamethasone, metaclopramide, diphenhydramine, and prochlorperazine, were administered before and after treatment with cisplatin. Timed-collections were obtained by continuous percutaneous biliary drainage during the Taxol infusion: 530 mL (0–6 hours), 344 mL (6–12 hours), 211 mL (12–18 hours), and 34 mL (18–24 hours). In addition, four timed-collections were collected over the 24-hour period following the Taxol infusion: 330 mL (0–6 hours), 492 mL (6–12

hours), 109 mL (12–18 hours), and 287 mL (18–24 hours).

Quantification of Taxol and Taxol Metabolites in Bile

Detection and isolation of metabolites in bile were accomplished by the use of high-performance liquid chromatography (HPLC). The HPLC equipment is composed of a model 510 pump, a U6K injector, and either an M481 wavelength detector or an M991 photodiode array (Waters Associates, Milford, Mass.). The M481 wavelength detector was used at 235 nm, a wavelength that permitted detection of Taxol and metabolites in quantities as low as 50 pmol. In all cases 3–10 μ L of bile was injected directly into the analytical HPLC column (0.39 \times 25 cm Altex ODS C18 column) and eluted with a mixture of methanol and water (60:40, vol/vol) at a flow rate of 1 mL/min. The concentrations of Taxol (labeled X in rats and IX' in the patient) and each Taxol metabolite (labeled I, V, VI, and VII in rats, and VI', VII', and VIII' in the patient) were quantitated from bile collected during all collection periods using linear calibration curves made with each of these pure compounds. The concentrations of the other minor metabolites (II, III, IV, IV', and V') were estimated taking the absorbance value of Taxol as a reference.

Purification of the Metabolites

Metabolites were purified by pooling bile samples and extracting the samples twice with equal volumes of ethyl acetate. The extracts were then evaporated to dryness under nitrogen and dissolved in a mixture of methanol and water (65:35, vol/vol). Next, separation was achieved by semipreparative HPLC using a 0.78 \times 30-cm reverse phase μ -Bondapak C18 column (Waters Associates), which was protected by a μ -Bondapak C18 guard column and a mobile phase consisting of a mixture of methanol:water (65:35, vol/vol) at a flow rate of 1 mL/min. Fractions containing each metabolite obtained during successive separations were combined. Further purification of the metabolites was achieved by analytical HPLC using a 0.46 \times 25-cm ODS Altex 5- μ m column, and a mobile phase consisting of a mixture of methanol and water (60:40, vol/vol) that flowed at a rate of 1 mL/min.

Structural Identification of Metabolites

Metabolites were identified with mass spectrometry using a FinniganMat TSQ700 mass spectrometer (San Diego, Calif.) in fast atom bombardment (FAB) and desorption chemical ionization (D/CI) modes. Each compound is fragmented in ions characterized by their m/z ratio (mass/charge). The charge being equal to 1 in this study, the ratio m/z directly gives the mass of each ion. Structural identification of metabolites was also accomplished with ¹H-nuclear magnetic resonance (¹H-NMR) using a Bruker 400-MHz spectrometer (Wissembourg, France).

RESULTS

Detection of Taxol and Metabolites in Rat and Human Bile

To detect the presence of hydrophilic metabolites, unextracted bile samples were initially studied by HPLC. In both rat and human bile samples collected after treatment, several compounds absorbing at 235 nm (the peak wavelength of absorption of Taxol and taxane derivatives) were identified (Fig. 1 A-B, curve a). These peaks were identified in neither pretreatment bile samples (Fig. 1A-B, curve b) nor in bile samples obtained from rats that were injected with the formulation vehicle alone (Fig. 1A, curve c). In rats, 10 different peaks (labeled I to X) corresponding to unmetabolized Taxol and Taxol metabolites were identified in posttreatment bile samples, and six different peaks (labeled from IV' to IX') were identified in posttreatment human bile. The HPLC retention times of these peaks were not affected following incubation of rat and human bile samples with sulfatase and β -glucuronidase. This indicated that these peaks corresponded to neither sulfated nor glucuroconjugated Taxol derivatives (12). In addition, the magnitudes of these absorption peaks were not modified, and additional peaks were not apparent following incubation with the enzymes. These results indicated that hydrophilic glucuroconjugated metabolites were not present in the void volume of the HPLC column.

Purification and Characterization of Taxol Metabolites in Rat and Human Bile

The compounds corresponding to each new absorption peak identified by HPLC were subsequently purified. The peaks labeled X in rat bile and IX' in human bile were identified as unmetabolized Taxol. After purification, these compounds exhibited identical characteristics as the Taxol reference compound, including identical retention times on analytical HPLC and identical UV spectra (absorption peaks at 235 and 275 nm). Moreover, the D/CI mass spectra of these compounds and the Taxol reference compound were identical, with prominent fragment ions at m/z 286 (side chain at C-13), 447 (taxane ring), and 569 (taxane ring with the side chain at C-2), and FAB mass spectra revealed identical protonated molecular ions at m/z 854.

The structures of metabolites were preliminarily identified by FAB and D/CI mass spectrometry. There were no protonated molecular ions of these metabolites with masses ranging from 886 to 1500 U. With the exception of metabolite I that was detected in rat bile only, each of the other metabolites has a taxane ring (prominent fragment ions at m/z 447 or 463), a side chain attached to the C-13 position of the taxane ring (prominent fragmentation at m/z 286 or 302), and a benzoate group attached at the C-2 position of the taxane ring (prominent fragment ion at

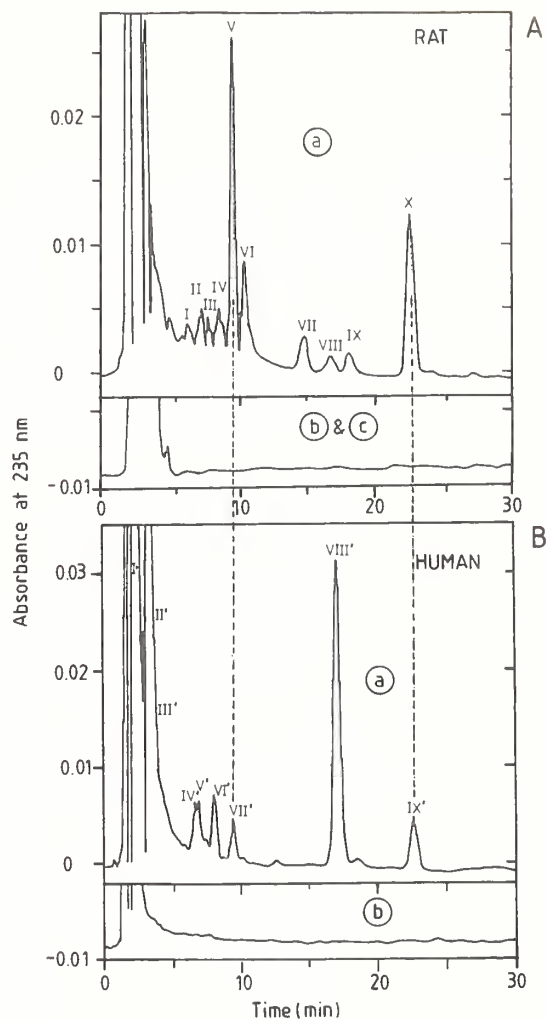


Fig. 1. HPLC analysis of bile samples. Unextracted bile samples (3 μ L) were injected directly onto the HPLC column. (See "Materials and Methods" section.) **A.** Rat bile samples: (a) Chromatograph tracing of a bile sampled 1 hour after Taxol treatment. Taxol metabolites correspond to peaks labeled I to IX. Unmetabolized Taxol corresponds to peak X. (b) Chromatograph tracing of a pretreatment bile sample. (c) Chromatograph tracing of a bile sample obtained 1 hour after the IV administration of 2 mL of the Taxol formulation containing a mixture of polyethylene glycol hydroxystearate, dimethylsulfoxide, and 0.9% saline (1:1:8). **B.** Human bile samples: (a) Chromatograph tracing of bile collected during the first 0-6 hours following the end of the 24-hour infusion of Taxol. Taxol metabolites correspond to peaks labeled IV' to VIII'. Unmetabolized Taxol corresponds to peak IX'. (b) Chromatograph tracing of a pretreatment bile sample.

m/z 569 or 585 corresponding to the taxane ring and the side chain at C-2). Metabolite I had a prominent protonated molecular ion at m/z 587 (FAB mass spectrometry) indicating that it lacked the side chain at the C-13 position of the taxane ring. This metabolite was identified as baccatin III after comparison to a baccatin III reference compound. It demonstrated identical analytical characteristics as the baccatin III reference com-

pound, including identical retention HPLC times, identical UV spectra (maximal absorption peaks at 232 and 275 nm), and identical mass spectra in both FAB and D/CI modes. Baccatin III was determined to be a minor biliary metabolite, accounting for less than 5% of all taxanes found in rat bile.

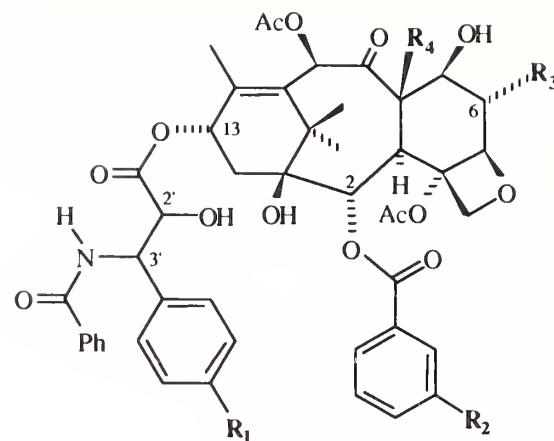
The protonated ions of metabolites V, VI, and VII in rat bile and metabolites VII' and VIII' in human bile were at m/z 870, 16 mass units greater than the protonated molecular ion of Taxol (m/z 854). Initially, these results indicated that these metabolites may be monohydroxylated. Similarly, the protonated molecular ions of metabolite III in rat bile and metabolite VI' in human bile were at m/z 886, 32 mass units greater than that of Taxol, suggesting that they were dihydroxylated metabolites.

Structural Identification of the Major Metabolites

The structures of the major metabolites of Taxol were then identified using both mass spectrometry and nuclear magnetic resonance spectroscopy. The chemical structures of these metabolites are depicted in Fig. 2. Mass spectrometry of metabolite VII in rat bile and metabolite VIII' in human bile revealed identical fragment ions at m/z 286, which corresponded to the C-13 side chain on the taxane ring. Both compounds also had another identical fragment ion at m/z 463. The mass of this fragment ion was 16 units greater than that of the fragment corresponding to the taxane ring (m/z 447) of the Taxol reference compound. A comparison of the $^1\text{H-NMR}$ spectrum of Taxol with the spectra of metabolites VII and VIII' confirmed these results. Moreover, the $^1\text{H-NMR}$ spectrum of metabolite VII revealed the presence of a hydroxyl group on methyl C-19 at position C-8 of the taxane ring, and the $^1\text{H-NMR}$ spectrum of metabolite VIII' revealed the presence of a hydroxyl group on the α -position at C-6 of the taxane ring.

The fragment ions corresponding to the C-13 side chain (m/z 286) and the taxane ring (m/z 447) of metabolite VI in rat bile and Taxol were identical. The fragment ion corresponding to the taxane ring and the C-2 side chain (m/z 585), however, was 16 mass units greater than that of Taxol (m/z 569). A comparison of the $^1\text{H-NMR}$ spectrum of metabolite VI with that of Taxol confirmed that metabolite VI had a hydroxyl group on the C-2 side chain. The $^1\text{H-NMR}$ spectrum of metabolite VI also confirmed the presence of a hydroxyl group on the *m*-position of the phenyl group at C-2 (Fig. 2).

Identical HPLC retention times and mass spectra in both FAB and D/CI modes indicated that metabolite V in rat bile and metabolite VII' in human bile were identical. Their protonated molecular ions had masses (m/z 870) 16 mass units greater than that of Taxol. The fragment ions corresponding to the taxane ring and C-2 side chain of both compounds were identical to that of Taxol (m/z 569). Moreover, in both compounds, the fragment ion corresponding to the side chain at C-13 showed an excess of 16 mass units (m/z 302) by comparison with that of



	R ₁	R ₂	R ₃	R ₄
Taxol = X = IX'	H	H	H	CH ₃
V or VII'	OH	H	H	CH ₃
VI	H	OH	H	CH ₃
VII	H	H	H	CH ₂ OH
VI'	OH	H	OH	CH ₃
VIII'	H	H	OH	CH ₃
Baccatin = I	13-OH	H	H	CH ₃

Fig. 2. Chemical structures of Taxol and Taxol metabolites. Metabolites I, V (= VII'), VI, and VII were observed in rat bile (HPLC profile A in Fig. 1). Metabolites VI', VII' (= V), and VIII' were detected in human bile (HPLC profile B in Fig. 1).

Taxol (m/z 286). The $^1\text{H-NMR}$ spectra of both metabolites V and VII' revealed the presence of a single hydroxyl group at the *p*-position of the phenyl group at C-3' on the C-13 side chain (Fig. 2).

The structure of metabolite VI' in human bile was identified as a dihydroxylated compound after the mass of its protonated molecular ion was demonstrated to be 32 units greater than that of Taxol. Mass spectrometry (D/CI mode) demonstrated the presence of a hydroxyl group both on the C-13 side chain (fragment ion at m/z 302 compared with the corresponding fragment ion of Taxol at m/z 286), and on the taxane ring (fragment ion at m/z 463 compared with the corresponding fragment ion of Taxol at m/z 447). A comparison of the $^1\text{H-NMR}$ spectrum of metabolite VI' with the spectra of metabolites V and VIII' revealed that metabolite VI' was effectively dihydroxylated. Hydroxyl groups were identified at the *p*-position of the phenyl group at C-3' on the C-13 side chain and at the α -position at C-6 of the taxane ring (Fig. 2). Although both metabolite III in rat bile and metabolite VI' in human bile had an identical protonated molecular ion mass as that of metabolite VI', suggesting they were also dihydroxylated derivatives, the HPLC retention times

and mass fragment ions of these compounds were significantly different. This indicated that they had different chemical structures. The chemical structure of compound III was not determined.

Kinetics of Biliary Excretion of Taxol and Metabolites

Cumulative biliary excretion curves for both unmetabolized Taxol and metabolites during Taxol treatment and in the 24-hour posttreatment period are depicted in Fig. 3. In rats, the total biliary excretion of unmetabolized Taxol and metabolites in the 24-hour posttreatment period accounted for 40% of the total Taxol dose, and the total biliary excretion of Taxol and metabolites during the treatment and 24-hour posttreatment periods was significantly less (20%) in the patient. There were also significant differences between rats and the patient in the relative proportions of unmetabolized Taxol and metabolites excreted in bile. In rats, $12\% \pm 2\%$ of the total administered dose was recovered as unmetabolized Taxol during the period studied, whereas $3\% \pm 1\%$ was recovered as unmetabolized Taxol in the patient. Therefore, unmetabolized Taxol accounted for 30% and 15% of total biliary taxanes in rats and the patient, respectively. Moreover, there were also significant interspecies differences in the proportions of biliary metabolites as well as in the chemical structures of the metabolites themselves. For example, both rat and human bile contained a metabolite (metabolites V/VII') with a hydroxyl group substitution at the same position on the same phenyl group of the

C-13 side chain of the taxane ring. Metabolite V was the principal metabolite in rats, however, accounting for 33% of all taxane derivatives in bile and $13\% \pm 2\%$ of total drug disposition, and compound VII' was a minor metabolite in the patient, accounting for 10% of all taxane derivatives in bile and $2\% \pm 1\%$ of total drug disposition. On the other hand, metabolite VIII', which was not detected in rat bile, was the major biliary metabolite in the patient. This metabolite accounted for 60% of all taxane derivatives in the bile and $12\% \pm 2\%$ of total drug disposition in the patient.

Effects of Cytochrome P-450 Enzyme Inducers on Biliary Excretion of Hepatic Metabolites in Rats

The effects of various cytochrome P-450 enzyme inducers, such as benzopyrene, phenobarbital, and troleandomycine, on the hepatic metabolism and biliary excretion of Taxol was studied using male rats. HPLC profiles of bile collected in the 6-hour period following Taxol treatment did not demonstrate qualitative differences in the metabolites between rats pretreated with these cytochrome P-450 inducers (Fig. 4) and control rats that were not pretreated (Fig. 1A). In addition, there were no significant quantitative differences in the biliary excretion of unmetabolized Taxol between rats pretreated with the inducers and control animals. However, the ratio of the minor biliary metabolites (metabolites I, VII, VIII, and IX) to major metabolites (metabolites V and VI) increased in rats that were pretreated with phenobarbital. In the 6 hours following Taxol treatment in rats pretreated with the inducer phenobarbital, major and minor biliary metab-

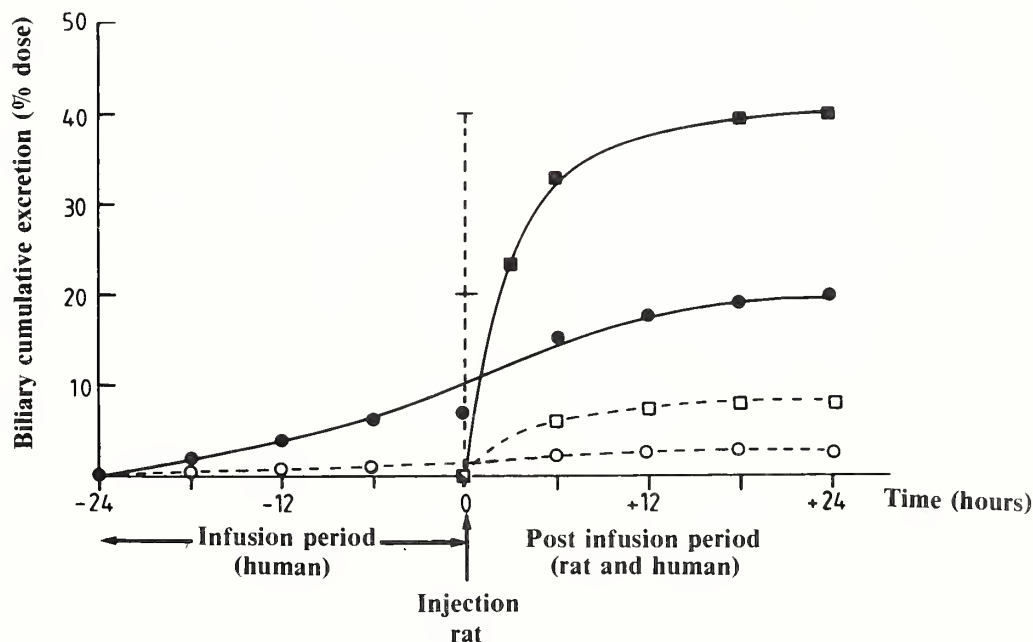


Fig. 3. Biliary excretion of Taxol in rats and in the human patient. Solid lines: cumulative amounts of Taxol and Taxol metabolites excreted in rat bile (■) and in human bile (●). Dashed lines: cumulative amounts of unmodified Taxol excreted in rat bile (□) and in human bile (○). Bile samples were injected directly without extraction into the HPLC column and the amount of each metabolite was calculated. (See "Materials and Methods" section.)

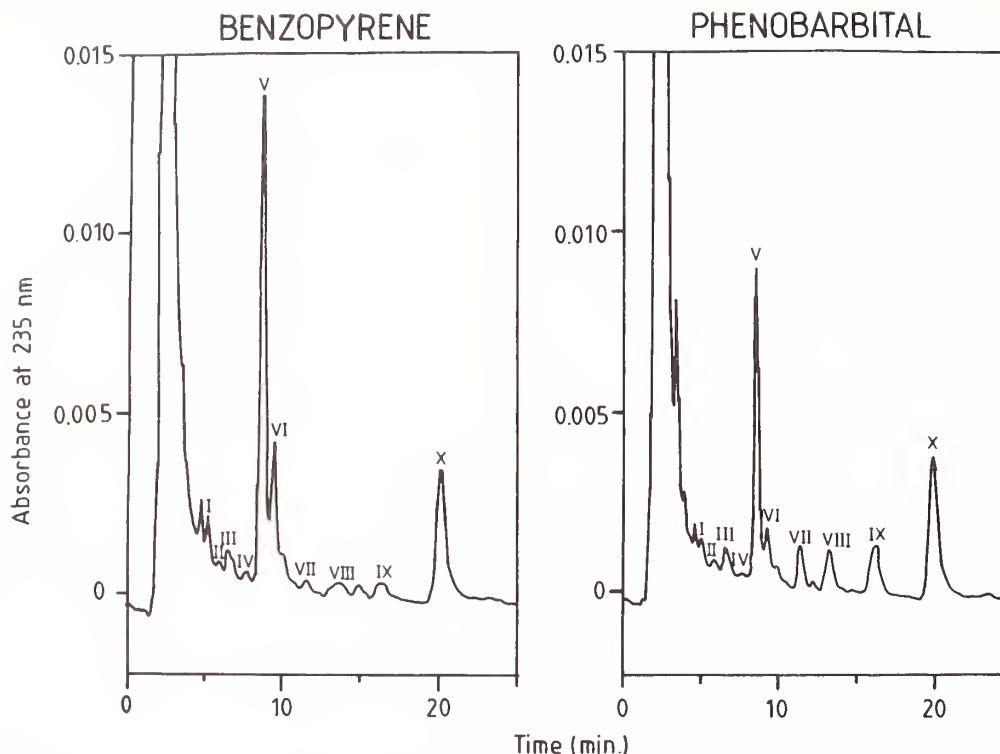


Fig. 4. HPLC analysis of bile samples obtained from rats pretreated with benzopyrene and phenobarbital. Left: HPLC profile of a bile sample from a male rat treated with benzopyrene. This profile was identical to the HPLC profile of a similar bile sample obtained from a control male rat treated with Taxol only. Right: HPLC profile of a bile sample from a male rat treated with phenobarbital. In both cases, bile samples were obtained 1 hour after Taxol treatment. A typical HPLC profile of a control male rat bile sample obtained 1 hour after Taxol treatment is shown in Fig. 1A. In all cases, bile samples were injected directly without any extraction into the HPLC column.

olites accounted for 8% and 4% of total drug disposition, respectively; these percentages were 16% and 1% in rats that were not pretreated with inducers.

Biliary metabolites excreted during the 6-hour period following treatment with Taxol were qualitatively similar in male and female rats. Although the total biliary excretion of unmetabolized Taxol and metabolites was not significantly different in male and female rats in the 6-hour posttreatment period ($20\% \pm 3\%$ versus $23\% \pm 3\%$ of total drug disposition, respectively), the relative proportions of unmetabolized Taxol and the major metabolites (metabolites V and VI) were different. The biliary excretion of unmetabolized Taxol was greater in female rats compared with male rats ($10\% \pm 2\%$ versus $5\% \pm 3\%$ of total drug disposition, respectively); the biliary excretion of major metabolites accounted for $13\% \pm 2\%$ and $12\% \pm 2\%$ of total drug disposition in males and females, respectively.

Effects of Cisplatin on the Biliary Excretion of Hepatic Metabolites in Rats

Biliary metabolites were qualitatively similar in both male and female rats pretreated with cisplatin before Taxol compared with rats that were not treated with cisplatin during the 6-hour period following Taxol treatment. Total biliary excretion (unmetabolized Taxol and

Taxol metabolites) was greater in female rats pretreated with cisplatin, however. The total biliary excretion of unmetabolized Taxol and Taxol metabolites accounted for $34\% \pm 3\%$ of total drug disposition in female rats pretreated with cisplatin, whereas total biliary excretion of unmetabolized Taxol and metabolites accounted for $23\% \pm 3\%$ of total drug disposition in female controls. In males, the total biliary excretion of unmetabolized Taxol and metabolites accounted for $20\% \pm 3\%$ of drug disposition in controls and $23\% \pm 3\%$ of total drug disposition in rats pretreated with cisplatin. In both male and female rats, pretreatment with cisplatin modified the biliary excretion of neither major nor minor metabolites. Instead, the increase in total biliary excretion was due to the enhanced biliary excretion of unmetabolized Taxol. In the 6-hour period following Taxol treatment, biliary excretion of unmetabolized Taxol accounted for $10\% \pm 2\%$ and $19\% \pm 2\%$ of total drug disposition in control and cisplatin-treated female rats, respectively. Respective values were $5\% \pm 2\%$ and $10\% \pm 2\%$ for male rats.

DISCUSSION

These studies constitute the first evidence that hepatic metabolism with biliary excretion of Taxol and Taxol metabolites accounts for a substantial proportion of the

pharmacological disposition of Taxol in both rats and a human. To date, nine Taxol metabolites have been detected in rat bile, and five metabolites have been detected in human bile. The chemical structures of four rat and three human metabolites have been identified thus far using mass spectrometry and ¹H-NMR spectroscopy. With the exception of baccatin III, a minor biliary metabolite in rats that lacks the side chain at the C-13 position of the taxane ring, the side chains at the C-2 and C-13 positions of the taxane ring on all the metabolites are intact. In both rats and humans, the principal biliary metabolites are hydroxylated. Of the nine metabolites found in rat bile, three are monohydroxylated metabolites, and one is a dihydroxylated metabolite. Similarly, two of the five metabolites found in human bile are monohydroxylated, and one is a dihydroxylated metabolite. The hydroxylations on the m-position of the phenyl group at the C-2 side chain (metabolite VI) and on the p-position of the phenyl at C-3' on the C-13 side chain (metabolite V/VII' and metabolite VI') are in concordance with the chemical reactivity of these aromatic groups. Interestingly, the derivative formed by the hydroxylation of the methyl group (C-19) at position C-8 of the taxane ring (metabolite VII) has also been identified in extracts of *Taxus* plants (14). In contrast, the hydroxylation of Taxol at taxane ring position C-6 (compounds VI' and VIII') has not been previously reported and would not have been predicted based on the chemical reactivity of this portion of the Taxol molecule.

Although the principal metabolites in rats and the patient are hydroxylated compounds, interspecies differences in the chemical structures of the principal metabolites are apparent. Only one of the four hydroxylated metabolites identified in rat bile is also found in human bile. This metabolite (metabolite V/VII'), which is hydroxylated on the phenyl group of the side chain at C-13 of the taxane ring, is the major biliary metabolite in rats, accounting for 13% of total drug disposition. This metabolite is only a minor biliary metabolite in humans, however, accounting for only 1% to 2% of the total drug disposition. Similarly, metabolite VI, which is hydroxylated on the phenyl group on the side chain at position C-2 of the taxane ring, accounts for 5% of total drug disposition in rats. This metabolite has not been detected in human bile, however. On the other hand, compound VIII', which is hydroxylated on the C-6 position of the taxane ring, is the major Taxol metabolite in human bile, accounting for 12% of total drug disposition, but this compound has not been detected in rat bile. Interspecies differences in the chemical structures of the dihydroxylated metabolites are also evident. These interspecies differences in the sites of hydroxylation suggest that different cytochrome P-450 enzymes may be involved in Taxol metabolism in rats and humans. It is also possible that these differences may, in part, be due to the modulatory effects on key metabolic processes by other ancillary medications given to the patient.

There were no qualitative differences in the biliary metabolites of Taxol in rats pretreated with various inducers

of cytochrome P-450 enzymes. Changes in the proportions of Taxol metabolites were noted only in rats pretreated with phenobarbital. Phenobarbital pretreatment resulted in an increase in the biliary excretion of minor hydroxylated metabolites, particularly metabolite VII, at the expense of major hydroxylated metabolites (metabolites V and VI). Male and female rats also demonstrated different excretory patterns: females excreted a greater proportion of unmetabolized Taxol into bile. In addition, pretreatment of male rats with cisplatin resulted in a modest increase in the biliary excretion of unmetabolized Taxol during the 6-hour collection period. This result concurred with previous studies demonstrating that cisplatin induces feminization of hepatic cytochrome P-450 expression and alteration of drug metabolism in rats (15,16).

Treatment of patients with cisplatin before Taxol has been demonstrated to induce more severe toxicity than the reverse sequence (11). These sequence-dependent effects have been attributed to a decrease in the systemic clearance of Taxol when Taxol treatment follows cisplatin (11). The studies described in this report do not clearly explain these sequence-dependent interactions on a metabolic basis; however, pretreatment of rats with cisplatin did not result in the reduced biliary clearance of unmetabolized Taxol nor in the increased biliary clearance of metabolites. It is still possible, however, that cisplatin may inhibit alternate pathways of Taxol metabolism that have not yet been identified, thereby accounting for the Taxol-cisplatin interactions observed in cancer patients. Such inhibition may result in a reduced systemic clearance of unmetabolized Taxol and higher concentrations of Taxol in both plasma and bile, all of which have been noted in both human and rat studies.

In summary, hepatic metabolism and biliary excretion appear to be a principal mechanism for the disposition of Taxol in rats and humans. In rats, approximately 40% of an administered dose of Taxol was recovered in bile as both unmetabolized Taxol and metabolites in the 24-hour period posttreatment compared with less than 10% recovered in urine as unmetabolized Taxol (12,17). Similarly, approximately 20% of an administered dose of Taxol was recovered in bile as unmetabolized Taxol and metabolites in the patient; renal disposition has been demonstrated to account for approximately 5% to 10% of total drug disposition (10,11). Because other metabolites have not been identified in plasma or in urine to date, it is likely that the bulk of drug disposition (i.e., 50% to 65% of an administered dose) is not metabolized. Similar to other antimicrotubule agents such as the vinca alkaloids, which exhibit an important biliary excretion, a substantial proportion of administered drug may avidly bind to cellular microtubules or even to hydrophobic cellular organelles as suggested by the subcellular binding of radiolabeled Taxol (18) and other fluorescent taxane derivatives (Wright M, Guénard D, unpublished observations). This conclusion is in agreement with the very large volume distribution of Taxol (mean 110 L/m²) that has been reported in early clinical trials (10).

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Taxol-Based Combination Chemotherapy and Other In Vivo Preclinical Antitumor Studies

William C. Rose*

Taxol, dissolved in cremophor/ethanol (50/50), followed by further dilution with saline, was successfully administered intravenously (IV) to mice bearing subcutaneously (SC) implanted murine Madison 109 lung carcinoma (M109), M5076 sarcoma, or seven different human tumor xenografts, including A431 vulva; A2780 ovarian; LX-1, H2981, and L2987 lung; and RCA and HCT-116 colon carcinomas. Taxol was active in all these distal site tumor models except the M5076 sarcoma. Schedule dependency and dose-response evaluations involving Taxol were studied in the SC M109 model. Taxol was given IV, and all treatments were of 7 days' duration. Each schedule was evaluated using several dose levels designed to incorporate the likely optimal (and maximum tolerated) dose(s). On the best schedule, daily injections for 7 days, Taxol exhibited a flat dose response; that is, good activity was obtained at Taxol dose levels that were only a fraction of its maximum tolerated dose. This profile provided an advantageous opportunity to evaluate Taxol-based combination chemotherapy. In a format in which Taxol was given every day on days 1 through 5, IV, and other drugs were given on days 1 and 5 (IV or intraperitoneally, IP) versus SC M109, dose titrations of each agent were evaluated singularly and in various Taxol-based combinations. The combination of Taxol plus cisplatin yielded a delay in tumor growth (17.8 days) that was minimally superior ($P < .05$) to the best delays caused by either drug alone (e.g., 13.5 days for Taxol); there was no enhancement of lifespan beyond that obtained using Taxol alone. Other Taxol-based combination chemotherapies, for example, Taxol plus VP-16, doxorubicin (Adriamycin), cyclophosphamide, methotrexate, pentamethylmelamine, bleomycin, or cimetidine, failed to produce therapeutically synergistic effects. Finally, a premedication regimen commonly used clinically to mitigate hypersensitivity reactions, that is, dexamethasone, diphenhydramine plus cimetidine or ranitidine, was evaluated in combination with Taxol. In mice implanted IP with M109, this premedication regimen failed to significantly or reproducibly modify Taxol's antitumor activity. [Monogr Natl Cancer Inst 15:47-53, 1993]

Despite the proven clinical utility of Taxol¹ (1), a convincing demonstration of its preclinical antitumor activity against stringent distal site tumor models has only recently emerged (2-4). Historically, Taxol had been found to be active when given intraperitoneally (IP) to IP-implanted tumors, and when given IP or subcutaneously (SC) versus human tumors xenografted within the subrenal capsule (5,6), but no reproducible activity was described in SC- or intravenously (IV)-implanted tumor models. The application of ethanol-based vehicles plus a suspending agent (e.g., cremophor or Tween 80) has allowed Taxol to be given IV against disseminated and distal site tumors with positive results. As a consequence of this development, we have been able to explore Taxol's schedule dependency, antitumor profile, and potential for therapeutic synergy when given with other cytotoxic drugs, in stringent tumor models.

Additionally, because Taxol's clinical formulation contains cremophor and there exist concerns regarding its use (7), the question has arisen as to whether the often applied premedication regimens (e.g., dexamethasone, diphenhydramine, and cimetidine or ranitidine) intended to reduce the adverse reactions also modify the antitumor activity of Taxol itself. We attempted to answer this query using an IP-implanted murine tumor model.

MATERIALS AND METHODS

Mice

Female Balb/c and (Balb/c \times DBA/2) F_1 (CDF₁) conventional mice and Balb/c-background athymic mice, 16 to 20 g, were purchased from Harlan-Sprague Dawley, Inc. (Indianapolis, Ind.). Feed and water were provided ad libitum. All studies involving these animals were conducted in accordance with our company guidelines.

Tumors

The murine Madison 109 lung carcinoma (M109) was serially maintained as an SC growing tumor in Balb/c mice. The following human tumors were serially maintained in athymic mice: A2780 ovarian; A431 vulva; HCT-116 and RCA colon; and LX-1, H2981, and L2987 lung carcinomas.

*See "Notes" section following "References."

Drugs

Bulk Taxol of >97% purity was dissolved in equal volume portions of cremophor and ethanol; dissolution was facilitated by sonification for 20 to 30 minutes. Stock solutions of Taxol prepared in this manner were kept refrigerated for as many as 9 days. As needed each day, stock solutions of Taxol were further diluted 1:4 with sterile saline such that the final working solutions were composed of Taxol in 10% cremophor-10% ethanol-80% saline. Diluted Taxol solutions were administered within 30 minutes of their preparation. This procedure allowed us to successfully administer Taxol IV at doses as great as 60 mg/kg in a volume corresponding to 0.01 mL/g body weight; however, the practical limits of Taxol's solubility in the final vehicle would suggest that doses in the 40 to 50 mg/kg range be considered as maximum. An exception to this Taxol preparation procedure was used for IP administration in the two IP M109 experiments performed and the IV injections used in the SC A2780 experiment. For these studies, stock solutions of Taxol were diluted 1:9 with sterile saline to yield final working solutions of 5% cremophor-5% ethanol-90% saline.

Doxorubicin, cisplatin, cyclophosphamide, bleomycin, methotrexate, pentamethylmelamine, diphenhydramine, dexamethasone, and ranitidine were prepared in saline; cimetidine was prepared in saline with a drop of Tween 80; and etoposide (VP-16) was suspended in carboxymethylcellulose and water. Doxorubicin was administered IV (0.01 mL/g body weight), and all the other drugs were administered IP (0.5 mL/mouse, with drug concentrations prepared based on the average body weight of each treated group).

Drug Evaluation

Detailed descriptions of the basic assay and evaluation methods used for the tumor models and experiments contained herein have been reported (8,9). Therapeutic results are presented in terms of 1) increases in lifespan reflected by the relative median survival time (MST) of treated (T) versus control (C) groups (i.e., % T/C values) and any long-term survivors; and 2) primary tumor growth inhibition determined by calculating the relative median times for T and C mice to grow tumors of a predetermined size (1 g for A2780 and M109 tumors, 0.5 g for all others) (i.e., T-C values). Tumor weights were interchangeable with tumor size on the basis of $1 \text{ mm}^3 = 1 \text{ mg}$. Statistical evaluations of data were performed using the Gehan's generalized Wilcoxon test (10). The activity criterion for increased lifespan was a T/C of $\geq 125\%$ and was applicable for both SC and IP M109 experiments. The activity criterion for tumor inhibition was a delay in tumor growth consistent with one gross \log_{10} cell kill (LCK). The absolute T-C value needed to attain this level of efficacy varied from experiment to experiment and depended on the tumor volume doubling time of the control mice in each study.

Group sizes typically consisted of eight mice, except for

six mice in the treated groups of the first of two IP M109 experiments. The various drug treatments used are described in conjunction with the experimental data. Drug-treated mice dying before their tumors reached target size were considered to have died from drug toxicity. Groups of mice with more than one death due to drug toxicity were not used in the evaluation of antitumor efficacy, and for each drug, per experiment, the highest dose tested that did not cause such lethality was termed the "maximum tolerated dose." For the experiments involving human tumor xenografts, tumor-bearing mice were sorted into treatment and control sets at a time posttumor implant such that all tumor weights ranged from 50 to 100 mg, and median tumor weights per set were reasonably similar. In every experiment, Taxol was evaluated at a minimum of three dose levels.

RESULTS

Taxol's Activity Versus Human Tumor Xenografts

With a common treatment schedule of a total of five injections, each given every 2 days ($q2d \times 5$), Taxol was administered IV to athymic mice implanted SC with one of seven different human tumors. In each instance, treatment was initiated in mice bearing small but established tumors. A summary of the optimal effects of Taxol in each tumor model is presented in Table 1.

Tumor growth delays ranged from about 15 days for the H2981 human lung carcinoma to greater than 50 days for the HCT-116 human colon carcinoma. Depending on the tumor volume doubling times of the various human tumors, the antitumor effects displayed by Taxol were consistent with between 1 and 5 LCK. In many of these experiments, Taxol was able to cause complete regression of the tumor masses, including several instances of tumor-free survival still apparent at termination (e.g., day 60 postimplant). The optimum effect of Taxol against the familiar LX-1 human lung carcinoma is shown in Fig. 1.

Taxol's Schedule Dependency and Dose Response Versus SC M109 Lung Carcinoma

Against established M109 tumors implanted SC 5 days earlier, Taxol administered IV was evaluated using four different treatment schedules. Each of the treatment schedules used: seven injections, given every day ($qd \times 7$); four injections, given every 2 days ($q2d \times 4$); three injections, given every 3 days ($q3d \times 3$); and two injections, given every 6 days ($q6d \times 2$), had an identical total duration of 7 days. Each schedule used was evaluated at five closely intervalled dose levels designed to encompass the likely optimal (and maximum) dose(s) for that treatment.

A maximum tolerated dose level was achieved using each schedule. Cumulative optimum doses ranged from 96

Table 1. Effect of Taxol versus established SC human tumor xenografts

Tumor	Type	Route, schedule	Optimum dose, mg/kg per injection	Maximum	
				T-C, days	LCK*
A2780	Ovarian	IV, q2d × 5; beginning on day 7	18	14.3	2.2
LX-1	Lung	IV, q2d × 5; beginning on day 5	24	37.3	4.9
H2981		IV, q2d × 5; beginning on day 5	24	14.8	1.3
L2987		IV, q2d × 5; beginning on day 14	36	26.0	2.6
RCA	Colon	IV, q2d × 5; beginning on day 4	36	>40	>1.7
HCT-116		IV, q2d × 5; beginning on day 3	36	>50	>2.6
A431	Vulva	IV, q2d × 5; beginning on day 3	36	36.8	2.4

*LCK derived for each experiment was based on the following tumor-volume doubling times: A2780, 2.0 days; LX-1, 2.3 days; H2981, 3.4 days; L2987, 3.0 days; RCA, 7.0 days; HCT-116, 5.7 days; A431, 4.8 days.

mg/kg to 180 mg/kg. Because of solubility constraints, we were unable to evaluate in excess of 60 mg/kg of Taxol per injection, and even solutions containing the Taxol concentration needed for these injections had a short working time (time between saline dilution and injection) and opalescent quality. A vehicle control group that received 0.01 mL/g of body weight of the Taxol vehicle IV, once a day for 7 days, suffered no deaths or weight loss that could not be attributed to tumor growth.

Efficacy was positively correlated with frequency of injection. Optimum therapy values obtained using the qd × 7, q2d × 4, q3d × 3, and q6d × 2 schedules, as measured by lifespan increases (% T/C values) and maximum delays in primary tumor growth (via T-C values in days), were as follows: 197% and 20.3 days; 180% and 15.0 days; 159% and 12.8 days; and 146% and 9.3 days, respectively. Each of these delays in tumor growth was consistent with ≥ 0.8 LCK.

The maximum tolerated dose for each treatment schedule is described with the graphical display of the delays in tumor growth caused by each regimen (Fig. 2). The better antitumor effects were clearly obtained with treat-

ment schedules involving frequent Taxol administrations (i.e., smaller intervals between injections). Efficacy was not, however, correlated with dose intensity per se, because cumulative Taxol exposure per unit time during the 7-day course of therapy was greater for some of the regimens that were among the least effective.

The good activity of Taxol versus SC M109 was obtained at dose levels that were only a fraction of its maximum tolerated dose. On the best schedule, qd × 7, Taxol exhibited a rather flat dose-response curve over the span of doses tested. Specifically, the % T/C (and T-C) values at the various dose levels evaluated, 36, 24, 18, 12, and 8 mg/kg per injection, were as follows: toxic (-); 174% (18.8 days); 182% (20.3 days); 197% (19.5 days); and 166% (13.0 days), respectively. The tumor growth delay responses are shown in Fig. 3.

It should be noted that 8 mg/kg per injection, qd × 7, which represented a cumulative exposure of 56 mg/kg of Taxol, yielded an increase in lifespan and delay in tumor

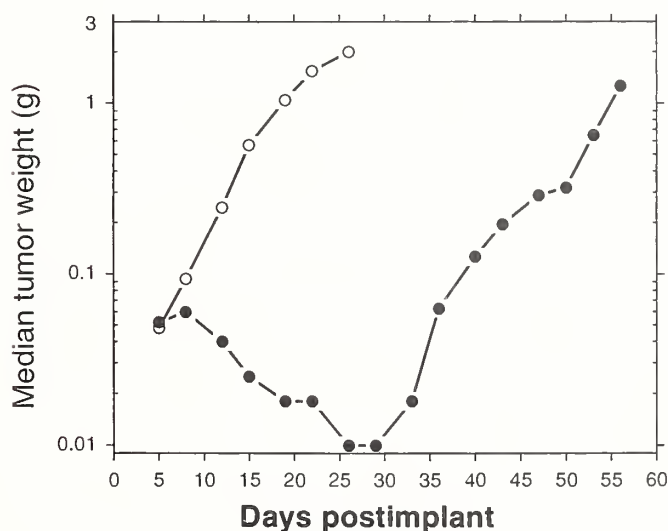


Fig. 1. Effect of Taxol versus staged SC LX-1 human lung carcinoma. Taxol, 24 mg/kg per injection, IV, q2d × 5 beginning on day 5 (●), and vehicle controls (○).

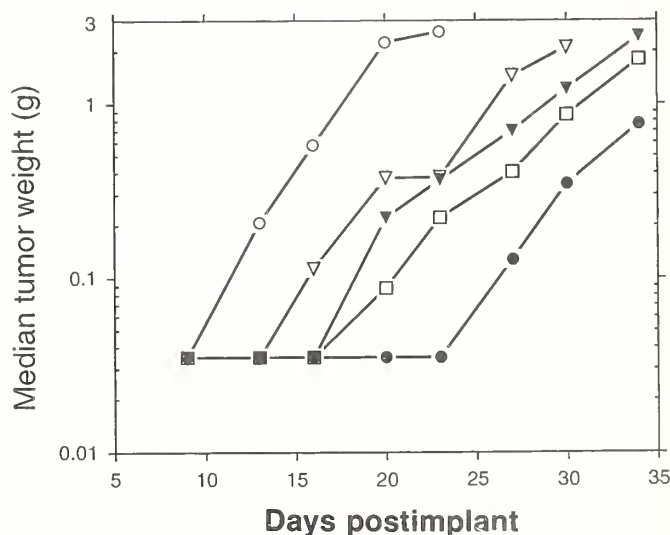


Fig. 2. Schedule dependency evaluation of Taxol versus staged SC M109 lung carcinoma. The maximum tolerated doses for each treatment used were as follows: qd × 7, 24 mg/kg per injection (●); q2d × 4, 48 mg/kg per injection (□); q3d × 3, 60 mg/kg per injection (▼); q6d × 2, 48 mg/kg per injection (▽); and vehicle controls (○). All treatments were IV beginning on day 5 postimplant.

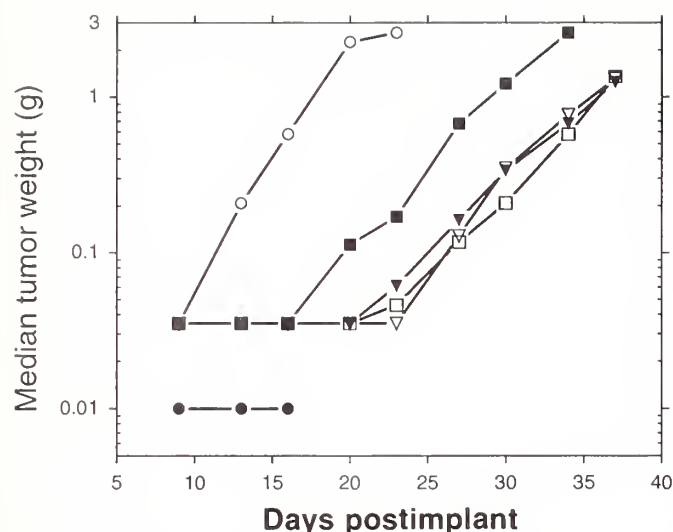


Fig. 3. Dose-response curves for staged SC M109 lung carcinoma treated with Taxol on a qd \times 7 schedule. The following doses (mg/kg per injection) were administered IV beginning on day 5 postimplant: 36 (\bullet), toxic; 24 (∇); 18 (\blacktriangledown); 12 (\square); 8 (\blacksquare); and vehicle controls (\circ).

growth similar to, or greater than, the best effects associated with more than two or even three times as much Taxol given on other schedules (e.g., q3d \times 3 or q6d \times 2).

Taxol-Based Combination Chemotherapy Versus SC M109 Lung Carcinoma

The shallowness of Taxol's dose-response curve in the SC M109 tumor model, when the drug was administered on a consecutive daily schedule, provided a useful basis for evaluating Taxol-based combination chemotherapy. One could reduce Taxol's dosage in a drug combination setting to, for example, one half of its maximum tolerated level and still achieve a nearly optimal antitumor effect. A summary of the optimal effects obtained in the SC M109 Taxol-based combination chemotherapy experiments performed is presented in Table 2.

In the initial three studies, Taxol was given every day on days 1 through 5 (qd1 \rightarrow 5), IV, and the other drugs evaluated were given only on days 1 and 5 (IV or IP). On the days (1 and 5) when both Taxol and another drug were given, Taxol was given 1 hour before the other drug. Each

Table 2. Taxol-based combination chemotherapy versus SC M109 lung carcinoma: Selected optimal therapeutic results

Taxol IV, qd1 \rightarrow 5	Treatment, mg/kg per injection		Maximum effect	
	Other Drug, route, schedule	Dose	MST, % T/C	T-C, days
<i>First experiment</i>				
48	—	—	147	13.5
—	Cisplatin, IP, days 1&5	8	123	6.0
—	VP-16, IP, days 1&5	120	126	11.5
36	Cisplatin, IP, days 1&5	6	155	17.8*
24	VP-16, IP, days 1&5	60	158	14.5
<i>Second experiment</i>				
36	—	—	166	10.8
—	Doxorubicin, IV, days 1&5	10	157	10.8
—	Cyclophosphamide, IP, days 1&5	160	139	6.0
36	Doxorubicin, IV, days 1&5	5	168	13.5
24	Cyclophosphamide, IP, days 1&5	80	161	11.5
<i>Third experiment</i>				
24	—	—	140	10.5
—	Methotrexate, IP, days 1&5	45	109	-0.5
—	Pentamethylmelamine, IP, days 1&5	180	85	-2.0
18	Methotrexate, IP, days 1&5	30	137	11.3
24	Pentamethylmelamine, IP, days 1&5	80	138	10.5
<i>Fourth experiment</i>				
24 [†]	—	—	145	13.0
—	Bleomycin, IP, qd5 \rightarrow 9	30U	110	5.0
—	Cimetidine, IP, qd5 \rightarrow 9	100	103	-0.5
24 [†]	Bleomycin, IP, qd5 \rightarrow 9	20U	128	17.5
18 [†]	Cimetidine, IP, qd5 \rightarrow 9	100	151	11.8

* $P < .05$ versus effect of Taxol alone.

[†]qd5 \rightarrow 9.

drug was evaluated singularly using a closely intervalled dose titration, and drug combinations were evaluated using various proportions of each drug's expected maximum tolerated dose.

In the initial experiment, cisplatin and VP-16 were each evaluated in Taxol-based combinations. The maximum effects for Taxol at its optimum dose of 48 mg/kg per injection were a 147% T/C and a 13.5-day T-C (which were greater than the maximum effects obtained with either cisplatin or VP-16 alone). The best effects obtained using Taxol plus cisplatin were a T/C of 155% accompanied by a 17.8-day T-C. This delay in tumor growth, but not the increase in lifespan, was significantly ($P < .05$) greater than the delay caused by Taxol alone. The therapeutic synergy suggested by this result occurred at only one specific dose combination, and it was a maximum tolerated level. The best effects obtained with Taxol plus VP-16, a T/C of 158% accompanied by a T-C of 14.5 days, were not superior to the optimum effects of Taxol alone.

In the second combination chemotherapy experiment, Taxol, doxorubicin, and cyclophosphamide were evaluated in two-drug, Taxol-based combinations. Taxol and doxorubicin singularly achieved similar maximum effects (170 to 173% T/C and each a 10.8-day T-C), whereas cyclophosphamide caused effects inferior to these two drugs. Optimal combination chemotherapy involving Taxol plus doxorubicin resulted in a maximum T/C of 175% and a maximum T-C of 13.5 days. For Taxol plus cyclophosphamide, a maximum T/C of 161% and an 11.5-day T-C were obtained. These combination chemotherapy results were not significantly superior to the best effects of the individual drugs.

In the third study, methotrexate and pentamethylmelamine were individually tested in combination with Taxol. Neither of these two drugs was active in the SC M109 tumor model when two injections were administered IP 4 days apart. No combination of Taxol plus either methotrexate or pentamethylmelamine yielded therapeutic results superior to that caused by Taxol alone (i.e., 140% T/C and 10.5-day T-C).

In the fourth experiment performed, Taxol was given every day on days 5 through 9 (qd5→9) IV against established M109 tumors, and bleomycin was given IP using the same schedule. When both drugs were administered in combination, bleomycin preceded Taxol by 30 to 60 minutes. Bleomycin was not active using this treatment regimen. Taxol alone achieved a maximum T/C of 145% and a 13.0-day T-C. Taxol plus bleomycin failed to significantly ($P > .05$) enhance the activity associated with Taxol alone, but the most efficacious dose combination caused a 17.5-day T-C, which was almost statistically meaningful.

Effect of Premedication (Diphenhydramine, Dexamethasone, and Cimetidine or Ranitidine) on Taxol's Activity Versus IP M109 Lung Carcinoma

Mice implanted IP with M109 were treated with dexamethasone IP 6 and 18 hours prior to Taxol; diphenhydramine plus either cimetidine or ranitidine were

given IP 30 minutes prior to Taxol; and Taxol was given IP on days 5 and 8 postimplant. The doses used for the premedication drugs ranged between 50% and 233% of the estimated mouse equivalents to clinical dosages. A summary of the two experiments performed according to this protocol is shown in Table 3.

In the initial IP M109 experiment, Taxol alone achieved a maximum T/C of 179% at 50 mg/kg per injection; a greater dose of 75 mg/kg per injection (evaluated in duplicate) was too toxic, and a lower dose of 30 mg/kg per injection was just barely active. None of the other drugs was active when applied individually. The maximum T/C values achieved with Taxol in combination with dexamethasone and diphenhydramine, plus either ranitidine or cimetidine, were 221% and 259%, respectively. Although these T/C values were greater than the maximum T/C value obtained with Taxol alone, they were not statistically different ($P > .05$). Also of interest was the observation that a dose of Taxol, 30 mg/kg per injection, which by itself was only minimally active, was potentiated by the premedication to become as effective as optimal individual Taxol therapy of 50 mg/kg per injection.

The suggestions of enhanced therapeutic activity seen in the first experiment prompted a reevaluation with slightly larger group sizes. In the second experiment, Taxol alone achieved a maximum T/C of 244% at 50 mg/kg per injection; a dose of 75 mg/kg per injection was too toxic. None of the drugs composing the premedication regimen was active on its own. Premedication with dexamethasone and diphenhydramine, plus either ranitidine or cimetidine, failed to modify the maximum antitumor activity of Taxol or potentiate the activity of suboptimal doses.

Taxol plus cimetidine were also evaluated against staged SC M109 (Table 2). Taxol's activity was not enhanced by daily pretreatment (30 to 60 minutes) with cimetidine on a qd × 5 schedule.

DISCUSSION

The IV administration of Taxol in cremophor-ethanol-saline vehicles has allowed for the expression of substantial antitumor activity in stringent distal site solid tumor models of both murine and human origin. Previous reports (5,6) of Taxol's ineffectiveness against most distal site tumors were probably a consequence of the insolubility of Taxol in nearly all the vehicles used in those earlier studies.

Using one of the tumor models in which Taxol had shown reproducible activity, SC M109, a schedule dependency study was conducted that included closely titrated doses, escalation to frankly lethal levels, and identical total durations of therapy per schedule. Daily Taxol administration was superior to every-other-day treatment, which, in turn, was more effective than intermittent injections with intervals of still greater magnitude. Even suboptimal dose levels used on the daily treatment schedule were more effective than optimal doses applied with the intermittent injection schedules. Previous schedule de-

Table 3. Taxol in combination with a premedication regimen (diphenhydramine + dexamethasone + cimetidine or ranitidine) versus IP M109 lung carcinoma

Treatment (mg/kg/inj), days 5 and 8, IP				
Taxol	Diphenhydramine	Dexamethasone	Cimetidine (C) or Ranitidine (R)	MST % T/C
<i>First experiment (n = 6/group)</i>				
75	—	—	—	109;132
50	—	—	—	179
30	—	—	—	129
—	32	6	200 (C)	94
—	32	6	32 (R)	94
75	32	6	200 (C)	259
30	32	6	200 (C)	188
75	32	6	32 (R)	221
30	32	6	32 (R)	182
<i>Second experiment (n = 8/group)</i>				
75	—	—	—	103
50	—	—	—	244
30	—	—	—	138
—	32	6	200 (C)	109
—	32	6	32 (R)	100
75	32	6	200 (C)	Toxic
50	32	6	200 (C)	209
30	32	6	200 (C)	138
75	32	6	32 (R)	100
50	32	6	32 (R)	225
30	32	6	32 (R)	163

pendency studies conducted under the auspices of the National Cancer Institute involved Taxol administered IP to mice bearing IP-implanted P388 leukemia (6). Although a fractionated dose schedule, eight injections given every 3 hours, was found to be quite effective, the Taxol dose levels used with single-bolus and intermittent injection schedules were not escalated beyond 9 mg/kg per injection, and no obvious maximum tolerated dose was attained; thus, definitive schedule dependency characterization is not possible. Multiple injections per day for several days may be worth evaluating in the SC M109 model, as would constant infusions, but they are technically more difficult to conduct in the mouse given the solubility constraints surrounding Taxol, as well as the irritating nature of the cremophor/ethanol-containing vehicle to the tail vein.

The SC M109 tumor model was also used to investigate Taxol-based combination chemotherapies for therapeutic synergy. The gradual slope of Taxol's dose response in this model would portend well for detecting potential therapeutic synergies because one could reduce the dosage of Taxol used in the combination setting to, for example, only half the maximum tolerated level and still expect to achieve a near optimal effect. Nevertheless, despite the use of Taxol in combination with many other drugs of different chemotypes, mechanisms of action, and dose-limiting toxicities, in various proportions to each other with respect to their individual maximum tolerated doses, no useful synergistic drug pair was found. For the initial three experiments, Taxol was administered 1 hour prior to the other drugs on days when both were given. The decision to

use this sequence of administration (albeit with a different interval between drugs) stemmed from the data of Citardi et al. (11) and Rowinsky et al. (12). They found that in vitro exposure of L1210 cells to Taxol and cisplatin was most effective (greatest cytotoxicity) when Taxol was given (24 hours) prior to cisplatin (11), and that a more profound neutropenia was observed clinically in patients receiving cisplatin prior to Taxol, relative to the reverse sequence, perhaps because of a 25% lower Taxol clearance rate when cisplatin was given initially (12). In the fourth experiment, having had little or no success with the Taxol followed by another drug sequence, we reversed the order of administration, but no dramatic outcome was observed.

Tumor growth delays in modest excess (e.g., 4.5 days) of those achieved individually by Taxol, or by any of the other drugs evaluated, were obtained by Taxol plus cisplatin and Taxol plus bleomycin. Only in the former situation was the combination's best effect significantly greater than the maximum effects of the individual drugs. In practical terms, the enhanced delay in primary tumor growth (lifespan was not increased) was, even if experimentally reproducible, of limited likely utility.

In light of the inability to demonstrate a meaningful Taxol-based therapeutically synergistic drug combination, it would seem prudent to expand the search to other tumor models, schedules of treatment, and drugs.

Administration of Taxol clinically has been associated with occasional instances of (potentially severe) hypersensitivity reactions. It is not known whether such reactions are due to Taxol, to cremophor (in the vehicle), or to both

agents. To prevent or mitigate the hypersensitivity, it is recommended that patients be given a premedication regimen consisting of an H_2 -histamine antagonist such as cimetidine or ranitidine, an H_1 -histamine antagonist, diphenhydramine, and an anti-inflammatory agent (e.g., dexamethasone). The possible influence of this premedication regimen on Taxol's antitumor activity was investigated using the staged IP M109 tumor model. The dosages of each agent used prophylactically in the clinic (7) were converted to equivalent amounts for mice (by multiplying the mg/kg dose in humans by 12, which assumes equivalency on an mg/m^2 basis), and these amounts were further increased by approximately 50% to 233% to provide a stringent assessment of their potential for interaction.

In the initial experiment performed, the premedication regimen appeared to have potentiated both Taxol's maximum effect and the effect of suboptimal Taxol doses. Although the maximum increase in lifespan was greater in the drug combination setting compared with Taxol alone, the difference was not statistically different ($P > .05$). The lack of influence of the premedication regimen on Taxol's antitumor activity was subsequently confirmed in a second study with larger group sizes.

Taxol has been found to have broad-spectrum antitumor activity in distal site murine and human solid tumor models. The successful demonstration of such efficacy is probably a consequence of Taxol's dissolution in cremophor/ethanol, which allowed, on dilution with saline, its IV administration. Schedule dependency studies clearly supported the advantage of a once-daily treatment schedule rather than less frequent intervals of injection. The activity advantage was observed despite the greater dose intensity and cumulative Taxol exposure sometimes associated with those less effective schedules. No Taxol-based combination chemotherapy was meaningfully more efficacious than the best therapeutic result obtained with an individual drug (usually Taxol) in the combination. Taxol plus cisplatin or bleomycin showed hints of therapeutic synergy, with the former combination showing mild statistical support for that statement, but further evaluations are required to provide a self-convincing demonstration of a Taxol-based synergy. Finally, a premedication regimen commonly recommended for its use with Taxol to prevent hypersensitivity reactions failed to alter significantly or reproducibly the antitumor activity of Taxol.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Taxol: Mechanisms of Action and Resistance

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Information on the mechanisms of action and of resistance to Taxol, as well as new data from our laboratory on the promoter regions of the genes that encode P-glycoprotein in a murine Taxol-resistant cell line, is discussed. Taxol induces the formation of stable bundles of microtubules, thereby interfering with the normal function of cellular microtubules. The drug can induce the multidrug-resistance (MDR) phenotype that includes the overproduction of P-glycoprotein, a membrane glycoprotein that acts as a drug efflux pump. In human tumors resistant to Taxol, P-glycoprotein could be responsible for maintaining the drug below cytotoxic levels. Analyses of the MDR promoters that are involved in P-glycoprotein expression and overproduction revealed an interesting recombination event in a Taxol-resistant cell line. As an important new clinical agent for the treatment of malignancies, Taxol requires further mechanistic investigations at the preclinical level. [Monogr Natl Cancer Inst Monogr 15:55-61, 1993]

The unusual chemical structure of Taxol¹ provided the impetus to undertake studies on the mechanism of action of this drug in the late 1970s. Taxol, at low concentrations, was found to be a potent inhibitor of eukaryotic cell replication. The drug blocked cells in the G2/M phase of the cell cycle. Analysis of such cells by electron microscopy and indirect immunofluorescence with monoclonal antibodies prepared against α - or β -tubulin revealed the presence of an unusual microtubule cytoskeleton that contained numerous microtubules, most of which were present in discrete parallel arrays that formed within the cell (1). As can be seen in Fig. 1, incubation of human ovarian SKOV3 cells with 1 μ M Taxol for 5 hours resulted in the formation of stable microtubule bundles. These bundles are diagnostic of Taxol treatment and are the result of the reorganization of the microtubule cytoskeleton. The microtubules present in bundle formations are extremely stable and do not depolymerize in the cold as do normal cellular microtubules. When cells are depleted of adenosine triphosphate (ATP), there is no microtubule bundle formation, although Taxol binds to the microtubules and stabilizes them (2). Such results suggest that there are two distinct steps involved in bundle formation and that the latter requires an intact cell with normal ATP levels. Although other antimitotic drugs such as colchicine and the vinca alkaloids have been described, only Taxol induces the formation of microtubule bundles within cells, thereby representing a new class of drugs with

a unique mechanism of action. Studies with 3T3 cells indicated that there was a single set of high-affinity binding sites to which Taxol bound in a specific and saturable manner. Elimination of microtubules from cells by depolymerization with colchicine or vinblastine resulted in a major decrease in Taxol accumulation within the cell. All of our data have strongly suggested that microtubules are a specific target for Taxol (3).

Experiments have been done in our laboratory both with cells growing in tissue culture and with purified tubulin in vitro; these methods have been complementary and have added to our understanding of the action of Taxol. Tubulin, purified from calf brain, can be assembled into microtubules in a test tube using the proper conditions that include the presence of microtubule-associated proteins (MAPs), guanosine triphosphate (GTP), ethylene glycol-bis-(beta) aminoethyl ether N-N¹ tetraacetic acid (EGTA), and organic buffer, at 37°C (4). Taxol has profound effects on this reaction, allowing assembly to take place in the absence of MAPs, GTP, and EGTA, and even at 4°C (5,6). As observed in cells, microtubules assembled in the presence of Taxol are stable to cold temperature and Ca⁺⁺, both of which normally depolymerize microtubules in vitro. Careful analysis by electron microscopy of the microtubules formed in the presence of Taxol indicated that they were shorter than microtubules assembled in the absence of drug; an approximate fourfold increase in the initiation phase of microtubule assembly had occurred. This correlated well with the fact that Taxol eliminated the 3- to 4-minute lag period normally observed during the in vitro assembly of microtubules. The evidence strongly suggested that Taxol was capable of altering the normal equilibrium that exists between the α - and β -tubulin dimers and microtubules, shifting it in favor of the microtubule and thereby lowering the critical concentration of tubulin required to form microtubules (Fig. 2).

Taxol has a binding site on the microtubule, and when the drug interacts with the polymer, the microtubule is stabilized against depolymerization. The drug binds specifically and reversibly to a polymerized form of tubulin with a stoichiometry approaching one. Although other antitumor agents such as the vinca alkaloids are also antimitotic agents, only Taxol has a binding site on the

*See "Notes" section following "References."

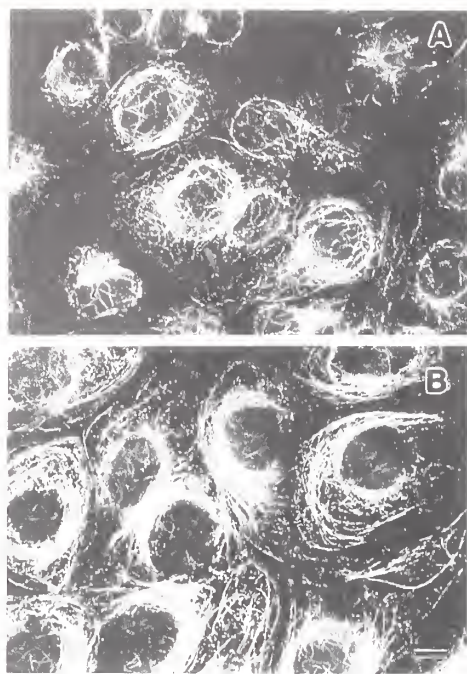


Fig. 1. Effect of Taxol on microtubule arrays in human ovarian SKOV3 cells. A, Control. B, Taxol-treated. Cells were grown on cover slips and incubated with either a final concentration of 0.1% dimethylsulfoxide (DMSO) (A) or 1.0 μ M Taxol prepared in DMSO (B) for 5 hours. Cells were washed with phosphate-buffered saline (PBS); treated with 0.5% Triton X-100 prepared in 100 mM piperazine-N, N'-bis[2-ethane sulfonic acid] (PIPES), 2 mM $MgCl_2$, and 2 mM EGTA for 4 minutes; washed with the same buffer; and fixed with 3% formaldehyde prepared in the same buffer for 40 minutes at room temperature (RT). Cells were incubated with a 1:100 dilution in PBS of a mouse monoclonal antibody against β -tubulin (Sigma Chemical Co.) at 37 °C for 1 hour, washed with PBS, and treated with a 1:40 dilution of fluorescein-conjugated goat antimouse IgG at RT for 1 hour. After the cells were washed with PBS, they were mounted in 33% glycerol containing 1 mg/mL P-phenylenediamine and viewed with a Zeiss Axioskop equipped with epifluorescent optics and a $\times 63$ oil immersion objective. Scale bar = 10 μ m.

intact microtubule, thereby distinguishing it from all other antitumor drugs (8).

Microtubules are an essential component of all eukaryotic cells and are required for the maintenance of cell shape, motility, and transport between organelles within the cell. This is in addition to their seminal role during cell division as a major component of the mitotic spindle. Microtubules are in a state of dynamic equilibrium with their subunits, the tubulin dimers. It would be expected that the introduction of Taxol, a drug that stabilizes microtubules, would result in major disruptions in cell division and other cellular activities that depend on microtubules (9).

To begin to decipher the binding site on the microtubule for Taxol, direct photolabeling of tubulin with radiolabeled Taxol has been undertaken (10). Our experiments indicate that Taxol preferentially binds covalently to the β -subunit of tubulin (Fig. 3).

RESISTANCE TO THE CYTOTOXIC EFFECTS OF TAXOL

Taxol-resistant cells were isolated over a period of many months from the murine drug-sensitive macrophagelike cell line, J774.2, by slowly increasing the concentration of drug in which the cells were maintained (11). The cell line that has been most extensively studied in our laboratory is J7.T1, which is approximately 900-fold resistant to Taxol and is maintained in 45 μ M of drug. It became clear during the analysis of these Taxol-resistant cells that they had the multidrug-resistance (MDR) phenotype (11,12). Considering the extreme hydrophobicity of Taxol and its natural product origin, it is not surprising that cells resistant to the drug had this phenotype.

Although most resistant to Taxol, the drug against which they were selected, J7.T1 cells demonstrated cross-resistance to other hydrophobic antitumor drugs such as the vinca alkaloids and doxorubicin. The use of radiolabeled Taxol made it clear that the resistant cells accumulated approximately 10% of the drug found in the sensitive cells (Fig. 4). This inability to accumulate Taxol was an important determinant in understanding the resistant phenotype.

Isolation and analysis of a plasma-membrane-enriched subcellular fraction from Taxol-sensitive and Taxol-resistant cells revealed the overproduction of P-glycoprotein in the resistant cells (Fig. 5). P-glycoprotein is thought to function as an energy-dependent drug efflux pump that maintains the drug within the cell below a cytotoxic level. Its overproduction results from the amplification and/or overexpression of a small MDR gene family. The glycoprotein is an integral membrane protein that passes through the membrane 12 times and has both its amino and carboxyl ends within the cell. A linker region separates the two rather homologous halves of P-glycoprotein, each of which contains a nucleotide binding site (13). ATP is thought to be hydrolyzed when drug is effluxed from the cell (14). Extensive studies are being done to determine the drug binding site in P-glycoprotein with the expectation that an understanding of the interaction of antitumor drugs with P-glycoprotein could lead to mechanisms for overcoming MDR (15).

In the mouse, there are two functional genes, *mdr1a* and *mdr1b*, each of which codes for a related but functionally distinct isoform of P-glycoprotein (16). The Taxol-resistant J7.T1 cell line is unusual in that it is the only multidrug-resistant cell line that has been studied in which both *mdr1a* and *mdr1b* are amplified and overexpressed and their gene products are overproduced in essentially equal quantities (12,17). The significance of this observation is not clear and may be unique to the J7.T1 cell line.

The presence of P-glycoprotein in J7.T1 cells is responsible for its Taxol-resistance phenotype. However, this may not be the only determinant of Taxol resistance.

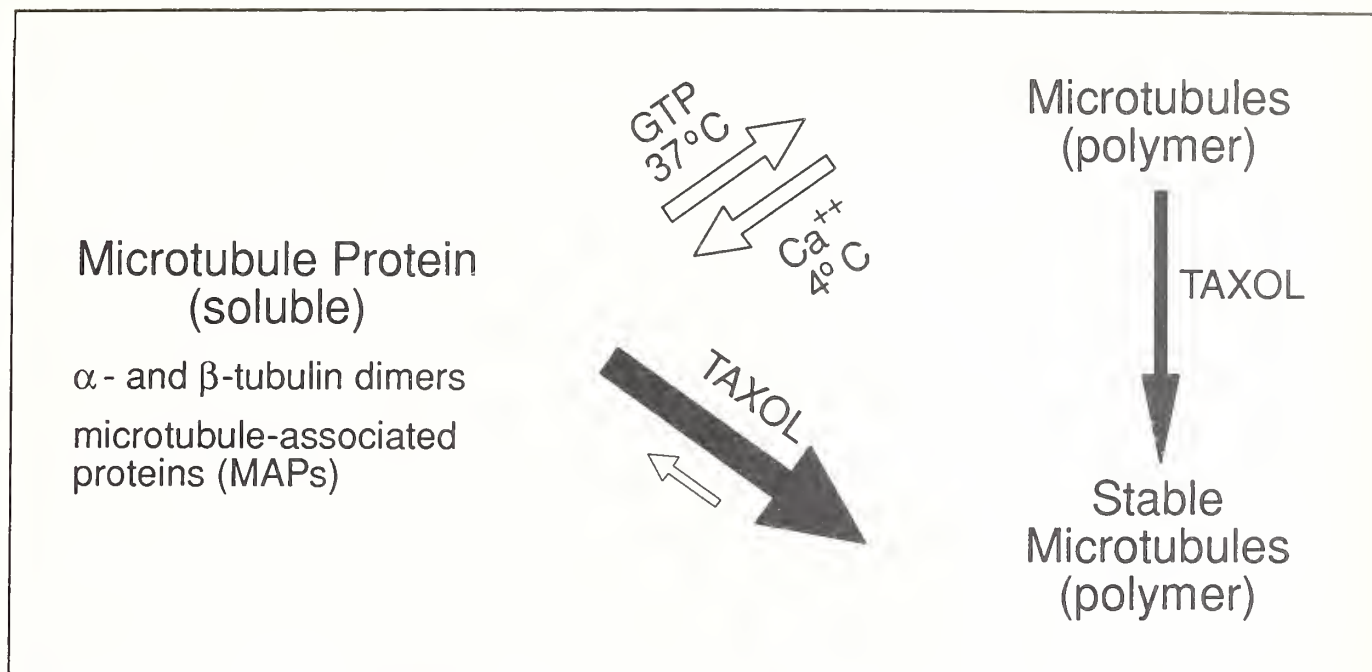


Fig. 2. Taxol alters the normal equilibrium between soluble tubulin dimers and polymerized microtubules. From Horwitz (7), with permission.

Studies in our laboratory indicate that the J7.T1 cell line is partially dependent on Taxol for growth (Rao S: unpublished data). Taxol-dependent cell lines, as well as a series of mutant Chinese hamster ovary cells that demonstrate resistance to Taxol and may have altered α - and/or β -tubulin subunits, have been described previously (18). Such Taxol-resistant cells are thought not to be the result of altered drug binding sites but rather to have tubulin alterations that influence the assembly and disassembly properties of the tubulin/microtubule system. Mutations involved in the destabilization of microtubules could be responsible for Taxol resistance (19). At present, there is no information available on the mechanisms of resistance that may develop in human tumors being treated with Taxol. It is reasonable that tubulin mutations may be an important determinant of resistance in human tumors that manifest relatively low drug resistance.

CHARACTERIZATION OF THE MDR PROMOTERS IN J7.T1 CELLS

To identify possible mutations and structural alterations in the promoter regions of the *mdr1a* and *mdr1b* genes, MDR promoter-specific probes (20,21) were used to examine several MDR cell lines. When *EcoRI*-digested genomic DNAs were hybridized to an *mdr1a* promoter-specific probe derived from a genomic clone, V1.1a (20), a novel amplified 4.3-kilobase fragment was detected in the Taxol-resistant cell line, J7.T1 (Fig. 6).

To characterize the 4.3-kb 5'-genomic fragment from the Taxol-resistant cell line, a complete *EcoRI*-digested genomic library from J7.T1 was constructed, and the

plasmid containing the 4.3-kb insert was isolated and designated T1.1a. Sequence analysis of the isolated clone and comparison with the previously characterized *EcoRI*-*mdr1a* genomic clone, V1.1a, which had been isolated from a vinblastine-resistant cell line genomic library, confirmed the identity of T1.1a as a 5'-4, 310-base pair genomic fragment of the *mdr1a* gene (Fig. 7).

The 3'-end of this clone consisted of the *mdr1a* promoter, the first noncoding exon, the first intron, the first coding exon, and part of the second intron. These sequences were identical with the sequences reported in V1.1a that spanned the same region. The sequences upstream of the common region between T1.1a and V1.1a contained two regions derived from the mouse LINE-1 repetitive element (-2468 to -3052). To identify the origin of the DNA stretch upstream of *mdr1a* in J7.T1, specific probes (*HindIII/BstEII* and *Clal/NcoI*) (see Fig. 7) were used to hybridize to two genomic clones that spanned different regions of the *mdr1b* gene (21). One of the genomic clones that contained *mdr1b* exon III and exon IV strongly hybridized to these probes (22).

The breakpoint in the *mdr1a* upstream region that corresponded to the integration site of the *mdr1b* fragment was the AT-rich most 3'-end of the LINE-1 element in V1.1a. AT-rich sequences have been found to be the preferred integration sites for retroposons and proviruses (23-25) and have been proposed as a recombination hotspot near the adenosine monophosphate (AMP) deaminase locus in Chinese hamster fibroblasts (26). These observations favor the hypothesis that the 3'-end of the repetitive element was the site of a recombination event in the Taxol-resistant cell line, J7.T1. The two regions of repetitivelike sequences in the DNA stretch orig-

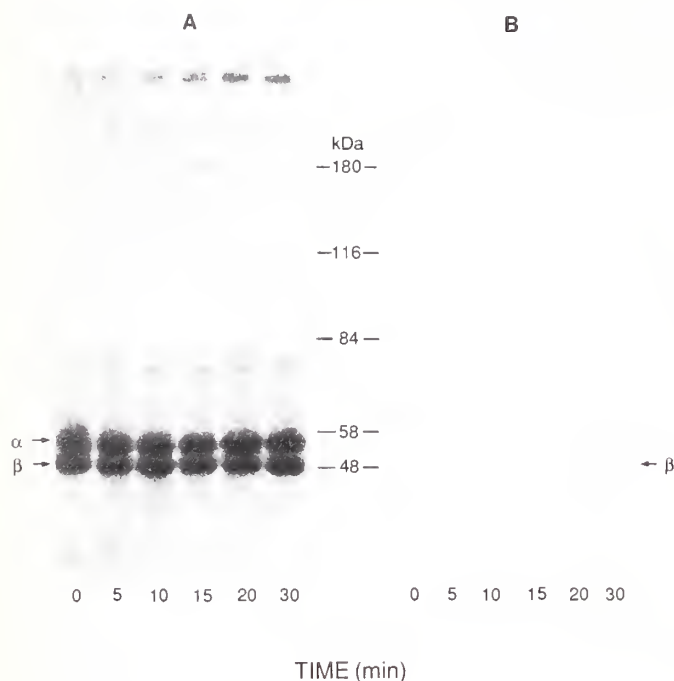


Fig. 3. Effect of ultraviolet irradiation on the binding of [^3H]Taxol to β -tubulin. [^3H]Taxol (final concentration $7 \mu\text{M}$) was added to microtubule protein ($11 \mu\text{M}$ tubulin), incubated for 20 minutes at 37°C , and exposed to UV light for the indicated time. At the end of each incubation, $30 \mu\text{L}$ was withdrawn, mixed with an equal volume of $2\times$ sodium dodecyl sulfate (SDS) sample buffer, and analyzed by SDS polyacrylamide gel electrophoresis (PAGE) and autoradiography. A, Coomassie stained gel. B, Autoradiograph of A. From Rao et al. (10), with permission.

inating from *mdr1b* in T1.1a were found to be homologous to the repetitive element in V1.1a. We have proposed that the homology between the upstream region of the *mdr1a* gene and the fourth intron of *mdr1b* favored a recombination event that resulted in the insertion of an *mdr1b* stretch of DNA upstream of the *mdr1a* in T1.1a (22). The three mouse MDR genes are clustered on chromosome 5 in the following order: *mdr1a*, *mdr1b*, and *mdr2* (27). A recombination event mediated by sequence homology such as an unequal chromatid exchange (28) is one possible mechanism that could explain the novel *mdr1a* 5' DNA fragment in J7.T1 cells.

It is not known if a single copy of the DNA rearrangement was present at an early time after exposure to Taxol and was subsequently further amplified in the selection process or if the DNA rearrangement took place at a later stage of exposure to Taxol. The significance of the rearrangement is not understood at this time but may be related to the equal overproduction of both isoforms of P-glycoprotein. The latter could have provided a selective advantage to the cells that allowed them to survive in the presence of Taxol. Although this rearrangement has been

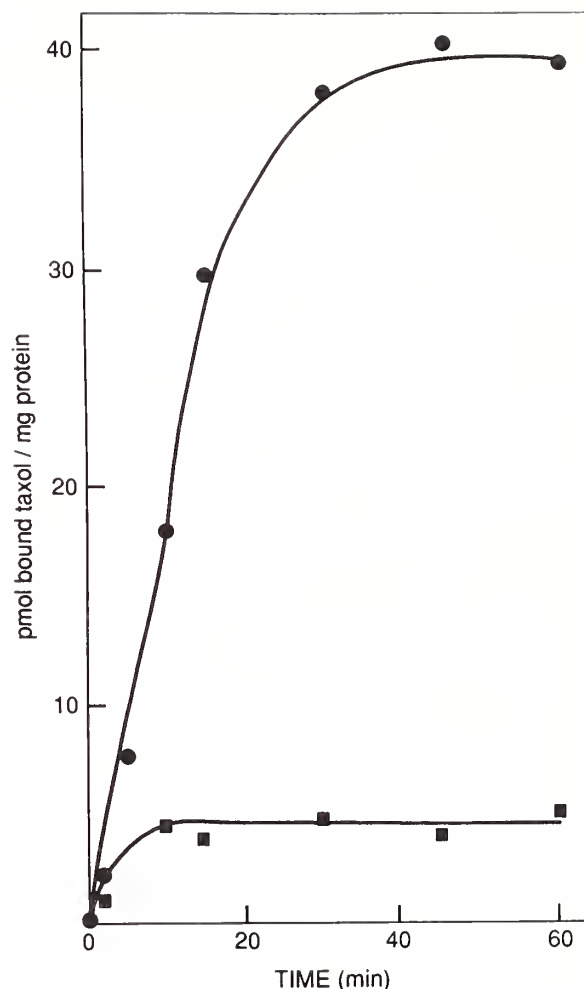


Fig. 4. Accumulation of [^3H]Taxol in J774.2 and J7.T1 cells. Confluent 35-mm plates of cells were incubated with 2 mL of medium containing $0.3 \mu\text{M}$ [^3H]Taxol at 37°C for the indicated times. Cells were washed three times with ice-cold PBS and lysed with 1 mL 1N NaOH for 16 hours. An aliquot of cell lysate was neutralized with an equal volume of glacial acetic acid, and radioactivity was determined. Control (●), J7.T1 (■). Each point represents the average of four determinations. From Roy and Horwitz (11), with permission.

documented in J7.T1 cells (22), there is no indication at this time to suggest that this or other rearrangements will be found in other Taxol-resistant cell lines or human tumors resistant to Taxol.

CONCLUSION

Although the clinical studies that have been done with Taxol are still small in number, all indications are that Taxol has the potential to become an important new drug for the treatment of human malignancies. The drug has a specific binding site on the microtubule, and when it interacts with this site, the microtubule is stabilized and unable to participate in normal microtubule functions within the cell. Taxol provides an excellent example of how knowledge concerning the mechanism of action of a drug can

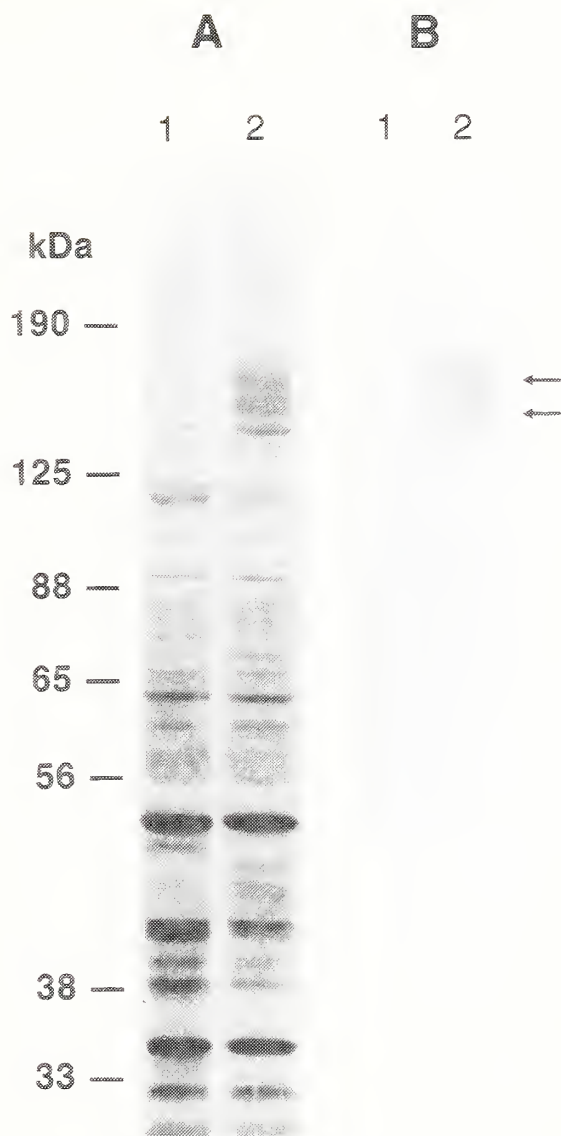


Fig. 5. Two isoforms of P-glycoprotein are overproduced in the murine Taxol-resistant J7.T1 cell line. Proteins from a plasma-membrane-enriched subcellular fraction were resolved by SDS-PAGE and silver-stained (A) or transferred to nitrocellulose (B). Twenty-five micrograms of protein was loaded in each lane. In B, the blot was probed with a P-glycoprotein-specific peptide polyclonal antibody (Oncogene Science). The figure shows parental drug-sensitive cells (murine J774.2 macrophagelike cells), Lanes 1, or Taxol-resistant J7.T1 cells, Lanes 2.

play an important role in encouraging clinical investigation. In addition, Taxol has provided a meaningful tool for studying the regulation and cellular functions of microtubules and for dissecting the complexities of drug resistance. In the laboratory, Taxol-resistant cells have been isolated that express the multidrug-resistance pheno-

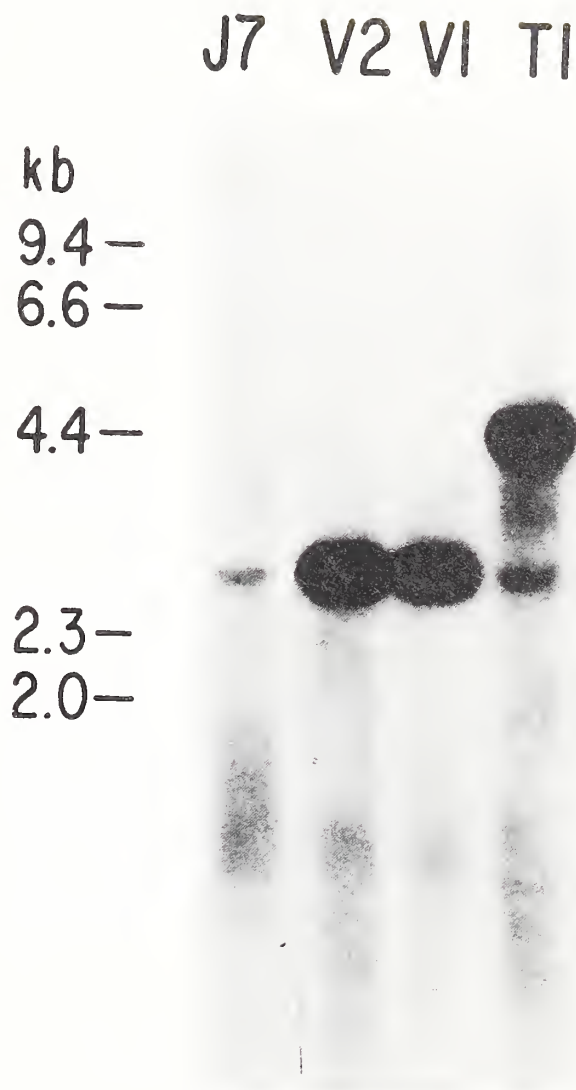


Fig. 6. Southern blot analysis of the *mdrla* promoter region in independently selected MDR J7 cell lines. *Eco*RI-digested genomic DNAs, isolated from drug-sensitive (J7), vinblastine-resistant (V1,V2), and Taxol-resistant (T1) cells, were analyzed using a *Nsi*I/*Sph*I (316-bp) probe derived from the *mdrla* promoter. Ten micrograms of J7 DNA and 1 μ g of V1, V2, and T1 DNA were analyzed. From Cohen et al. (22), with permission.

type, indicating that this may be one mode of resistance that will be present in human tumors. Taxol is a prototype for a new class of antitumor agents and has focused attention on natural products as a source of new drugs and on microtubules as a worthy target for cancer chemotherapeutic drugs.

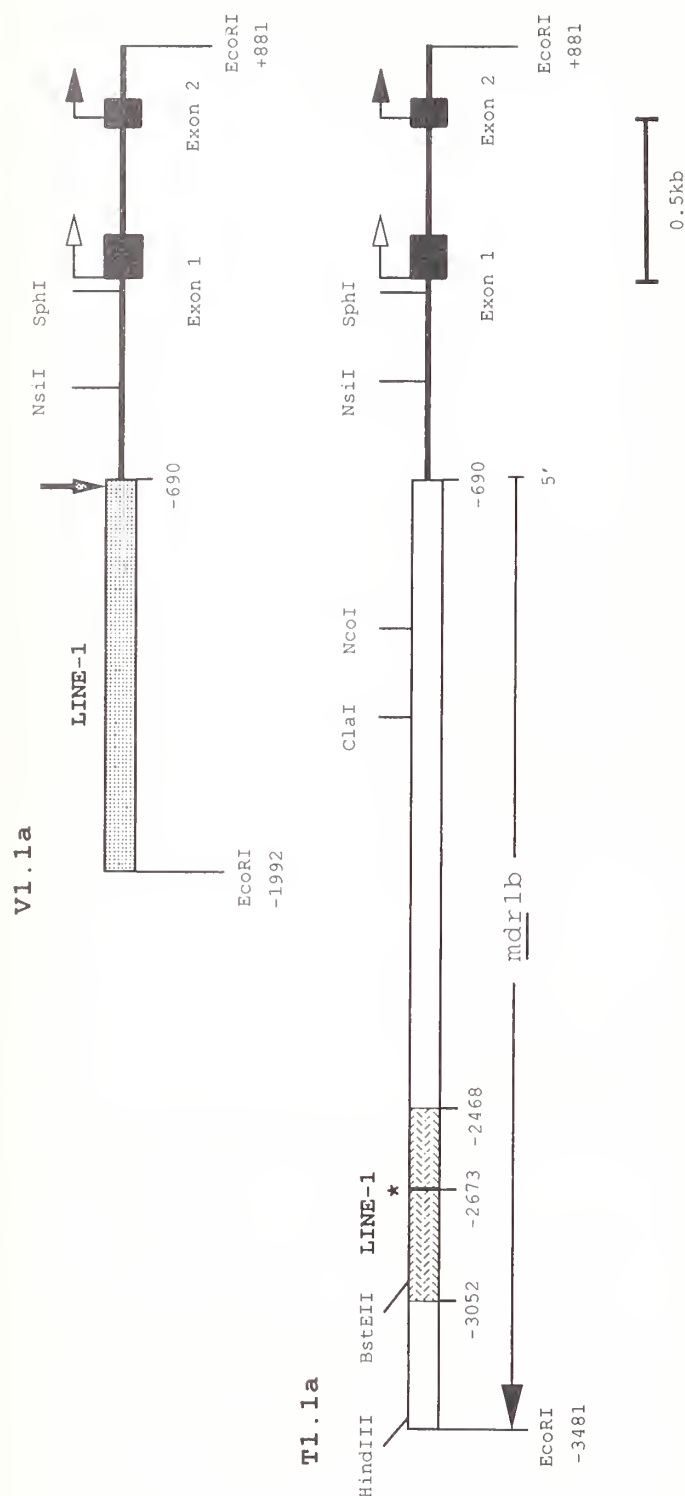


Fig. 7. Restriction maps of V1.1a and T1.1a 5'-genomic fragments. Exons are indicated by solid boxes, and repetitive elements are indicated by stippled boxes. The asterisk delineates two blocks of repetitive sequences. The open and filled arrowheads indicate transcription and translation initiation sites, respectively. The stippled arrow (pointing down) indicates the breakpoint at which the *Mdr1b* genomic fragment was inserted to create T1.1a. From Cohen et al. (22), with permission.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, NY).

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In Vitro Evaluation of Chemosensitizers for Clinical Reversal of P-Glycoprotein-Associated Taxol Resistance

Manfred Lehnert, Scott Emerson, William S. Dalton, Rita de Giuli, Sydney E. Salmon*

The purpose of this study was to estimate the potential usefulness of currently available chemosensitizers (CS) for clinical reversal of P-glycoprotein-mediated Taxol resistance. The 8226/DOX6 human myeloma cells were used to evaluate CS effects in serum-rich medium by means of the human tumor cloning assay. The 8226/DOX6 cells express low levels of P-glycoprotein as typically found in clinical cancer specimens and are approximately 40-fold resistant to Taxol when continuously exposed to the drug in serum-rich medium. The CS were used at maximum tolerated plasma levels (C_{max}) and at the concentrations achieved in human plasma by oral administration (C_{oral}). Of nine CS tested, cyclosporine A (CSA), verapamil (VER), quinidine (QD), and quinine (Q) were able to overcome Taxol resistance. QD and Q were effective at C_{oral} , whereas CSA and VER required C_{max} to significantly enhance Taxol cytotoxicity. The most potent agent was CSA, which increased sensitivity to Taxol by 8-, 12-, and 18-fold when used at concentrations of 1.0, 2.0, and 4.0 μM , respectively. At 5.0 μM , CSA was capable of fully normalizing Taxol sensitivity. On the basis of these data, infusional CSA might prove useful for clinical reversal of P-glycoprotein-associated Taxol resistance. It remains to be seen, however, whether the CSA concentrations needed to reverse Taxol resistance effectively can be safely achieved in human plasma when CSA is coadministered with Taxol. [Monogr Natl Cancer Inst 15:63-67, 1993]

The antimicrotubule agent Taxol¹ has shown promising clinical activity against various solid tumors, including platinum-refractory ovarian cancer (1) or metastatic breast cancer (2). One mechanism that can render cancer cells resistant to Taxol is P-glycoprotein-associated multidrug-resistance, also termed MDR1 (3,4). Various agents have been identified that are capable of overcoming MDR1 in vitro and in animal models (5). Most of these chemosensitizers (CS) have been described as being promising for clinical use, based on data from conventional in vitro studies. However, clinical effectiveness of CS has remained limited to date.

To better estimate the potential clinical usefulness of CS, we have previously developed an in vitro model that attempts to approximate clinical conditions by testing the CS in serum-rich medium at concentrations that can be achieved in human plasma, using MDR1 cell lines that express low levels of P-glycoprotein as typically found in clinical cancer specimens (6). In the present study, this in vitro model was used to evaluate the potential usefulness

of nine currently available CS for clinical reversal of P-glycoprotein-associated Taxol resistance.

MATERIALS AND METHODS

For in vitro chemosensitivity testing, the 8226/DOX6 human myeloma cells were used that exhibit all characteristics of the MDR1-phenotype (7). These particular variants previously have been shown to express P-glycoprotein at levels similar to myeloma cells from patients with drug-refractory disease (8).

The CS evaluated were the racemic mixture and R-enantiomer of verapamil (VER), cyclosporine A (CSA), amiodarone (AMD), quinidine (QD), quinine (Q), trifluoperazine (TFP), tamoxifen (TAM), and medroxyprogesterone acetate (MPA). Taxol was kindly provided by the Developmental Therapeutics Program, National Cancer Institute (Bethesda, Md.), and R-VER was provided by Knoll AG (Ludwigshafen/Rhein, Germany). All other drugs were obtained commercially. Taxol was supplied as a concentrated sterile solution of 6 mg/mL, formulated in 50% (vol/vol) polyoxyethylated castor oil (Cremophor EL[®]) and 50% dehydrated alcohol. The source of CSA was Sandimmune IV[®] (Sandoz), which also contains Cremophor EL as a vehicle. Q, QD, and TAM were purchased in powder form and dissolved in double-distilled water. The sources of all other drugs were the clinical formulations available for intravenous or intramuscular use. Final stock concentrations of either drug were prepared by using double-distilled water.

The CS were used at equimolar concentrations (2.0 μM) and at two dose levels of clinical interest: C_{max} , referring to the maximum tolerated plasma level in humans, and C_{oral} , defined as the concentration achievable in plasma by oral administration (Table 1). For some agents, C_{max} and C_{oral} were identical because maximum tolerated plasma levels can be achieved by oral administration. Selection of the particular CS concentrations was based on data published at the time this study was initiated. More recently, higher plasma levels of various agents have been achieved by escalated dosing in phase I/II MDR1 reversal studies. Accordingly, those agents were additionally tested at such higher concentrations.

The CS effects on Taxol-resistant myeloma cells were evaluated by using the human tumor cloning assay (13).

*See "Notes" section following "References."

Table 1. Clinically achievable CS concentrations*

Drug	C _{max}	C _{oral}
VER		
Racemic mixture	2.0	0.3
R-VER	2.0	0.3 [†]
TFP	0.3	0.3
CSA	1.0 [†]	0.2
AMD	2.0 [†]	2.0
QD	10.0	10.0
Q	20.0	20.0
MPA	2.0	2.0
TAM	2.0	2.0

*All concentrations are in μM .

[†]In recent MDR1 reversal studies, C_{oral} of R-VER was 2.0 μM (9); C_{max} of CSA was 1.0 and 4.0 μM when added to vinblastine (10) and VP-16 (11), respectively; and C_{max} of AMD was 7.0 μM (12).

We have previously described the use of the same myeloma cell lines and tumor cloning assay system to evaluate combined effects of CS on anthracycline and vinca alkaloid resistance (14). Studies were done in medium containing 10% fetal bovine serum (FBS) and in a serum-rich environment, by enriching the bottom and plating layers of the two-layer culture system with approximately 40% and 72% (vol/vol) serum, respectively. Specifically, the bottom layers contained 36% horse serum plus 3.5% FBS, and the plating layers contained 70% and 2%, respectively. Horse serum was the main serum type used because previous studies have shown excellent agreement between horse serum and human serum with respect to reducing the ability of various CS to reverse MDR1 in vitro (15). Exponentially growing cells were plated in triplicate at a concentration of 10 000 cells/35-mm culture dish. Drug exposure was continuous by incorporating the agents in the plating layer. Tumor cell colonies of 60 μM in diameter or greater were enumerated 14 to 21 days after plating, using an automated image analysis instrument optimized for tumor colony counting (16). The percent survival was calculated from the plating efficiencies of treated versus control cells. The IC₅₀ for Taxol was defined as the drug concentration that reduced colony formation to 50% of untreated cells. Sensitization factors were determined by dividing the IC₅₀ for Taxol alone by the IC₅₀s in the presence of CS. CS effects on Taxol resistance were evaluated only when the particular CS concentrations proved nontoxic to the cells when used alone. At each of the concentrations used, the CS had negligible effects on Taxol sensitivity in the parent cells.

RESULTS

Preliminary studies have shown the 8226/DOX6 cells to be approximately 12- and 40-fold resistant to Taxol relative to the parent cells when continuously exposed to the drug in 10% serum and serum-rich medium, respectively (data not shown). The resistance factors for Taxol in various experiments ranged from 9 to 13 and 35 to 65 in

10% serum and serum-rich medium, respectively. The main reason for these variations might be the exquisitely steep dose-effect curves of Taxol in both the parent and resistant cells. As a result, even minor differences in the doubling times of the cells may significantly alter Taxol sensitivity.

The equimolar potency of the CS in reversing Taxol resistance was determined by comparing the CS effects at 2.0 μM in medium containing 10% serum. Equimolar comparisons at higher CS concentrations were not possible because various agents became too toxic to the cells. AMD reduced Taxol resistance by approximately sixfold and was the most potent agent, followed by VER and QD (Table 2). However, CSA could not be evaluated at 2.0 μM in 10% serum because it was too toxic to the cells.

The next step was to evaluate CS activity at clinically achievable concentrations in medium containing 10% serum (Fig. 1). Under these conditions, QD was the most effective agent, followed by CSA at C_{oral}. CSA could not be analyzed at C_{max} because it was too toxic by itself. TAM, TFP, and MPA had negligible activity in reversing Taxol resistance (data not shown), as did VER when used at C_{oral}.

When using clinically achievable CS concentrations in a serum-rich environment, only QD, Q, CSA, and VER remained capable of increasing Taxol sensitivity (Fig. 2). Complete reversal of Taxol resistance with CSA or VER required the use of C_{max}, whereas both agents proved ineffective at C_{oral}. The use of high serum-protein concentrations completely abrogated the ability of AMD to reverse Taxol resistance. TFP, TAM, and MPA were also unable to enhance Taxol cytotoxicity (data not shown).

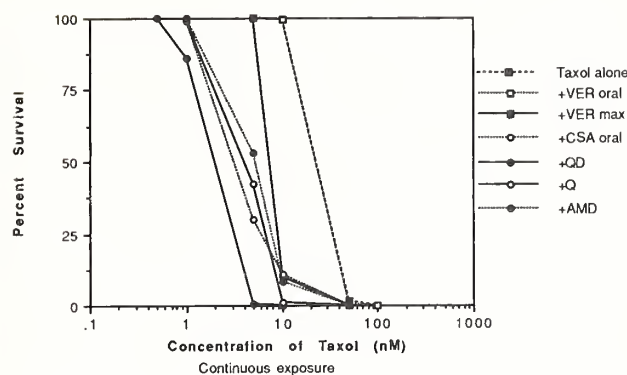
Finally, CSA, AMD, VER, and R-VER were tested at escalating concentrations (Fig. 3). Dose escalation resulted in a steep increase in effectiveness for CSA, VER, and R-VER, whereas AMD had minimal activity even at a concentration of 10 μM . At each dose level tested, CSA was more potent than VER in overcoming Taxol resistance. CSA at 1.0, 2.0, and 4.0 μM reduced Taxol resistance by approximately 8-, 12-, and 18-fold, respectively. At 5.0 μM , CSA was able to fully normalize Taxol sensitivity in the 8226/DOX6 cells.

Table 2. CS effects on Taxol resistance in 8226/DOX6 myeloma cells when used at equimolar concentration (2.0 μM) in medium containing 10% serum

CS	IC ₅₀ (nM)*	Sensitization factor
Taxol alone	28.9	
+ VER	9.3	3.1
+ AMD	5.0	5.8
+ QD	9.3	3.1
+ Q	17.7	1.6
+ TFP	20.8	1.4
+ MPA	14.6	2.0
+ TAM	21.1	1.4
+ CSA	NA [†]	

*Calculated as described in the "Materials and Methods" section.

[†]NA, not analyzed (CSA at 2.0 μM was too toxic to cells).



	Taxol	VER oral	VER max	CSA oral	QD	Q	AMD
IC ₅₀ (nM)	22.6	22.3	7.3	3.1	2.0	4.8	5.2
Sensitization Factor	-	1.01	3.1	7.2	11.6	4.7	4.3

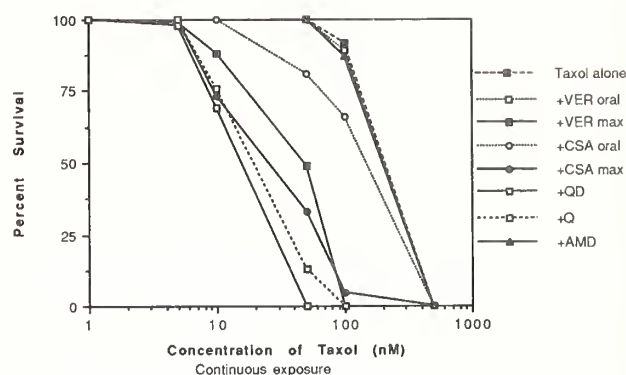
Fig. 1. Effects of CS on Taxol resistance in 8226/DOX6 cells when used at clinically achievable concentrations in medium containing 10% serum. QD, Q, and AMD were used at 10, 20, and 2.0 μ M, respectively. IC₅₀s and sensitization factors were calculated as described in the "Materials and Methods" section. Each point represents the mean of three replicates.

DISCUSSION

The purpose of this study was to estimate the potential usefulness of currently available CS for clinical reversal of P-glycoprotein-associated Taxol resistance. Specifically, we sought to identify the most promising CS to use in studies planned at the Arizona Cancer Center for patients with Taxol-refractory lymphoma or multiple myeloma.

We have previously observed VER, CSA, QD, and Q to retain the ability to reverse anthracycline or vinca alkaloid resistance in vitro when used at clinically achievable concentrations in a serum-rich environment (6). In the present study, the same four agents proved capable of overcoming Taxol resistance in the 8226/DOX6 cells when clinical conditions were approximated in vitro. Such pharmacologically guided in vitro modeling, like any other preclinical model, falls short of fully mimicking the complex clinical scenario. We nonetheless believe that this kind of simple in vitro evaluation of CS is closer to clinical reality than many other in vitro approaches and thus may be better able to predict clinical usefulness of CS.

QD and Q were the only agents capable of effectively enhancing Taxol cytotoxicity when used at concentrations that can be readily achieved by oral administration (17-20). Moreover, the particular concentrations used are usually well tolerated by the patients. These data are in accord with the reported ability of QD and Q to overcome Taxol resistance in the transgenic MDR1 mouse model developed at the National Cancer Institute (21). Nonetheless, QD and Q do not appear to be good candidates for effective clinical reversal of Taxol resistance. The two agents were far from being able to normalize Taxol sensitivity in the 8226/DOX6 cells, which express low levels of P-glycoprotein as typically detected in clinical cancer specimens. The chance for achieving plasma levels of QD and



	Taxol	VER oral	VER max	CSA oral	CSA max	QD	Q	AMD
IC ₅₀ (nM)	281	276	48.9	196	34.3	21	26.6	270
Sensitization Factor	-	1.02	5.8	1.4	8.2	13.4	10.6	1.04

Fig. 2. Effects of CS on Taxol resistance in 8226/DOX6 cells when used at clinically achievable concentrations in serum-rich medium. Concentrations of QD, Q, and AMD were 10, 20, and 2.0 μ M, respectively. IC₅₀s and sensitization factors were calculated as described in the "Materials and Methods" section. Each point represents the mean of three replicates.

Q that are significantly higher than the concentrations used in the present study seems limited because of the dose-limiting toxicities of the agents. Both cinchona alkaloids, in particular QD, can produce cardiac effects such as heart block or depression of myocardial function, which seems to limit their utility for co-administration with Taxol, which itself has been associated with cardiac toxicities (22).

A minimum concentration of 2.0 μ M was required of VER for producing a moderate (fourfold) reduction in Taxol resistance. Dose escalation resulted in a steep increase in effectiveness, and VER at 10 μ M was capable of normalizing Taxol sensitivity. However, VER plasma levels above 2.0 μ M frequently have been associated with serious cardiac toxicities or hypotension when using the racemic mixture and also the R-enantiomer of VER (9,23). Such cardiovascular activities render either form of VER poorly suitable for combination with Taxol.

CSA proved to be the most effective agent in reversing Taxol resistance in the 8226/DOX6 cells. Adding 1.0 μ M CSA resulted in an eightfold increase in Taxol sensitivity, using 4.0 μ M reduced resistance by 18-fold, and further dose escalation to 5.0 μ M was able to fully normalize Taxol sensitivity. The source of CSA used in these studies was Sandimmune IV, the CSA formulation available for clinical use. The vehicle used for the water-insoluble CSA in Sandimmune IV, is Cremophor EL, which has been demonstrated to reverse MDR1 effectively in vitro and in a murine model (24-26). It seems likely that Cremophor EL contributed to the activity of CSA in reversing Taxol resistance in this study. At a concentration of 33 μ g/mL, which is present at 2.0 μ M CSA when using Sandimmune IV, Cremophor EL has been able to partially reverse doxorubicin and vincristine resistance in 8226/DOX6 cells, MDR1 variants similar to the 8226/DOX6 cells used

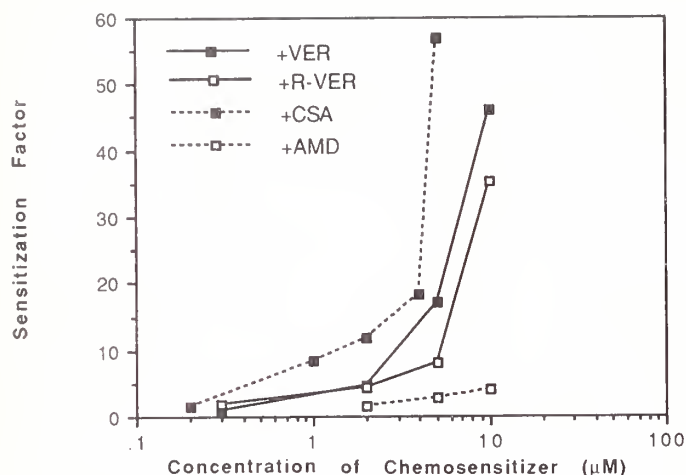


Fig. 3. Reversal of Taxol resistance in 8226/DOX6 cells by graded concentrations of CS. Cells were continuously exposed to drugs in serum-rich medium. Sensitization factors were calculated as described in the "Materials and Methods" section. Each point represents the mean of triplicate experiments.

in the present studies (24). Furthermore, using 2.0 μM Sandimmune IV has proved approximately twice as effective in reversing MDR1 as the same concentration of pure CSA (24). Finally, the ability of Cremophor EL to overcome MDR1 has been little affected by using high serum-protein concentrations (24).

The source of Taxol used in this study was the formulation available for clinical use, which also contains Cremophor EL as a solvent. The IC_{50} s of Taxol for the 8226/DOX6 cells were around 25 and 280 nM when used in 10% serum and serum-rich medium, respectively. These Taxol concentrations correspond to Cremophor EL dilutions of approximately 10^5 - and 10^4 -fold, respectively. A 10^4 -fold dilution has been shown to be the minimum concentration required of Cremophor EL for having some in vitro activity in reversing MDR1 (25,26). Nevertheless, significant Taxol resistance of the 8226/DOX6 cells was found in the present studies. Based on the peak plasma levels achieved for Taxol at maximum tolerated doses (4), clinical Taxol treatment may result in Cremophor EL plasma levels that are one to two orders of magnitude higher than the concentrations present in our studies. Such concentrations have been proved highly effective in reversing MDR1 (26). It thus is tempting to speculate that the solvent used in the clinical Taxol formulation might be capable of effectively overcoming P-glycoprotein-mediated Taxol resistance in human cancers.

In a recently reported phase I study, infusional CSA was able to achieve plasma levels of up to 4.0 μM when co-administered with etoposide (11). CSA concentrations in that range proved to be quite effective in reversing Taxol resistance in the present study. Because CSA and Taxol have differing organ toxicities, infusional CSA seems to be a promising approach for clinical reversal of P-glycoprotein-mediated Taxol resistance. It remains to be determined, however, whether MDR1 is indeed a mechanism involved in Taxol resistance of human cancers and

whether the cyclosporine concentrations needed to reverse Taxol resistance effectively can be safely achieved in human plasma when CSA is co-administered with Taxol.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Novel Taxol Formulations: Taxol-Containing Liposomes

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Taxol is a complex diterpenoid natural product under investigation for therapy of colon, ovarian, lung, and breast cancer, as well as for melanoma and lymphoma. One problem associated with the administration of Taxol is its low solubility; the formulation used clinically contains polyethoxylated castor oil (Cremophor EL®) and ethanol as excipients. Cremophor EL is implicated in hypersensitivity reactions observed on infusion of Taxol. To eliminate the Cremophor EL vehicle and possibly improve the antitumor efficacy of Taxol, a systematic approach was taken to formulate Taxol in phospholipid suspensions (liposomes). Prototype formulations were developed that have sufficient chemical and physical stability to test the hypothesis that liposomes can alter the pharmacology of Taxol, in addition to providing a biologically compatible carrier in which to administer the drug. In vitro, Taxol liposomes retain the growth-inhibitory activity of free Taxol against a variety of tumor cell lines. In vivo, preliminary results showed no effect of free Taxol (in Cremophor EL) on the growth of Colon-26, a Taxol-resistant murine tumor, when given at doses that included or exceeded the maximum tolerated dose (MTD). In contrast, Taxol liposomes delayed tumor progression at a dose that exceeded the MTD of free Taxol. [Monogr Natl Cancer Inst 15:69-78]

Taxol¹, a complex diterpenoid natural product (1) of the western yew, *Taxus brevifolia*, is under investigation as an anticancer agent (2-4) in phase I, II, and III human clinical trials. Target tumors include a variety of human cancers, including those of the colon, ovaries, lung, and breast, as well as melanoma and lymphoma. The subcellular target of Taxol action is microtubules, but Taxol is unique in its mechanism of action, showing a stabilization of microtubules rather than the disassembly of microtubules that is characteristic of the vinca alkaloid anticancer agents (5). It is thought that microtubule stabilization interferes with cellular progress through mitosis (6) and that this mechanism of action may be responsible for antitumor activity of the drug. A second notable property of Taxol is its poor solubility in aqueous media, which necessitates administration in a lipid vehicle. Presently, the vehicle used clinically is polyethoxylated castor oil (Cremophor EL®) containing 50% absolute ethanol. The Cremophor EL vehicle has been observed to cause serious, life-threatening anaphylactoid reactions in animals (7) and humans (3,4,8) and is physically incompatible with the components of some intravenous (IV) infusion sets, as evidenced by the extraction of plasticizers (9). Taxol often is given by IV administration as a slow (3- to

24-hour) infusion (3,4) to minimize vehicle-dependent toxicity, although shorter administration times are under investigation. Premedication with corticosteroids, antihistamines, and histamine H₂ receptor antagonists has reduced considerably the adverse reactions associated with Taxol administration (8,10); however, pharmacological intervention is less desirable than a safer, better-tolerated formulation. With multiple agents in general, and with the co-medication agents used with Taxol specifically, there exists considerable potential for drug interactions that could alter the pharmacokinetics and pharmacodynamics, and thereby the toxicity or efficacy, of Taxol.

Synthetic efforts have produced Taxol derivatives of higher aqueous solubility that retain antitumor activity (11,12), but as yet these analogues have not replaced the Taxol/Cremophor EL formulation clinically. The derivative Taxotere² (13) has entered human trial; solubility was reported to be 1.3-fold higher than that of Taxol, with approximately 2.5-fold higher activity in vitro (14). Given the low solubility of Taxol, the relatively small improvement with Taxotere may not overcome completely the problems associated with poor solubility.

The aim of our work is to improve the efficacy of Taxol-based anticancer therapy by reformulation of the drug in better-tolerated vehicles. Our primary goal is to eliminate the Cremophor EL vehicle, and the secondary goal is to modulate the pharmacology and toxicology of Taxol itself. Several modern drug carrier systems, including cyclodextrins, polyethylene glycol conjugates, and phospholipid vesicles (liposomes), presently are under evaluation to improve solubility or reduce dose-limiting side effects of other anticancer agents. Among these carriers, liposomes represent a mature, versatile technology (reviewed in 15-17) for improved solubilization of lipophilic drugs and are the subject of the present report. Preliminary results on the preparation and evaluation of prototype Taxol-liposome formulations will be presented here.

Rationale for the Development of Liposome Drug Carriers

Liposomes are spontaneously forming microparticulate carriers that are in clinical trial or under investigation as drug carriers for treatment of a number of neoplastic and infectious diseases (15-17). The widening variety of liposome-encapsulated drugs entering clinical trial reflects an emerging understanding of the safety, utility, and methodology required to produce the quantities of this

*See "Notes" section following "References."

experimental drug carrier required for human therapeutic trials. The applications envisioned for liposomes generally fall into two main categories (*reviewed in 15 and 17*): 1) Increase solubility of compounds that are poorly soluble in water; 2) alter the pharmacology of agents with desirable activity. The rationale for these applications is outlined below.

Formulation of poorly soluble drugs. Liposomes consist of one or more aqueous compartments contained within membrane bilayers. In most applications, the bilayer consists of naturally occurring or synthetic phospholipids, although a variety of amphiphilic molecules have been used to form liposomes. Because liposomes consist of a hydrophilic domain, a hydrophobic domain, and an interfacial region, they may accommodate therapeutic agents having diverse physical properties. Table 1 illustrates the characteristics of typical liposomes under development as drug carriers, similar to those tested in the present work (below). It is plausible to assume that well over 10 g of phospholipid may be administered safely to humans; 8- to 20-g doses of liposomes have been reported (*18,19*). Ten grams of lipid would represent a volume of approximately 12 mL of hydrocarbon phase (Table 1) (*20*). Therefore, a dose of Taxol of 125 mg/m² would be "dissolved" in the liposome membrane at a concentration of about 21 mM, approximately in the range of concentrations achievable with organic solvents such as methanol (data not shown).

Many current clinical and preclinical applications use liposomes or drug/phospholipid complexes as an aid in preparing better-tolerated formulations of hydrophobic, poorly soluble compounds. Examples of such agents include cyclosporin, amphotericin B, and muramyl tripeptide [*16*], and references therein; see below also]. Particularly noteworthy in the context of Taxol formulation is the incorporation of cyclosporin in liposomes (*21*). Cyclosporin has been administered to humans in the Cremophor EL vehicle, and acute toxic side effects of Cremophor EL have been observed (*22*). The liposome formulation showed immunosuppressive activity equal to that of the Cremophor EL-based formulation but with reduced renal and vehicle toxicity (*21*). In addition, greater compatibility with intravenous administration equipment was reported for the liposome/cyclosporin formulation. These results suggest clearly the utility and potential therapeutic gains from reformulation in liposomes of other drugs currently given in the Cremophor EL vehicle.

Alteration of pharmacology. A second major application of liposomes is to alter the pharmacology of biologically active agents. Two strategies by which such an objective may be accomplished are *site avoidance* and *site-specific delivery*. The aim of the former is to reduce

exposure to critical normal tissues while leaving intact the activity at the desired site of action. The aim of the latter is to enhance delivery to target tissue without enhancing unwanted toxicity. Both *passive* and *active* approaches have been taken to accomplish tumor targeting of liposomes. Passive site-specific delivery exploits either aberrations in physiology (e.g., extravasation of liposomes through compromised tumor vasculature) or the fortuitous property of liposomes having specific characteristics to localize in particular tissues (e.g., liposome clearance by cells of the reticuloendothelial system [RES]). Active targeting strategies center around the covalent linkage of ligands such as antibodies to the liposome surface in order to promote interaction predominantly with the target for which the ligand is selective (*23*). Although there is great potential for ligand-directed liposomes, particularly in conjunction with intracavitary therapy of malignancies (*24,25*), a number of fundamental enabling technologies require further development.

A third strategy to alter the pharmacology of drugs is *alteration of pharmacokinetics*. Although pharmacokinetics may be the major underlying mechanism by which site avoidance and site-specific delivery are accomplished, explicit mention here focuses attention on two important applications of liposomes: depot administration and intracavitary therapy. For depot administration, liposomes represent a biocompatible formulation tool for providing local sustained release, either from a single site of implantation, from long-circulating liposomes (*26-28*) in the blood, or from the dispersed sites in which liposomes may accumulate after systemic injection (e.g., cells of the RES may clear liposomes and subsequently release drug into the circulation). As for intracavitary therapy, liposome formulations may be of particular importance in the administration of Taxol. Direct intraperitoneal administration of chemotherapeutic agents has been proposed as a means to exploit pharmacokinetics for improved therapy of cancers that arise in or metastasize to the peritoneal cavity (*29,30*). To date, the clinical success of intracavitary therapy has been limited (*reviewed in 31*). Rapid absorption of drugs from the peritoneal cavity into the systemic circulation is a major hindrance to establishing high local concentrations of drug at the site of disease. An additional problem with poorly soluble drugs such as Taxol is that intraperitoneal precipitation could occur if the excipients used for solubilization are diluted or cleared from the peritoneal cavity more rapidly than the drug itself; precipitated drug may have negligible bioavailability. Drugs with the appropriate pharmacology for intracavitary therapy have been identified (*29*), and these should favor intraperitoneal effects over systemic side effects. As an alternate approach, particulate or colloidal drug carriers such as liposomes may enhance the efficacy of intracavitary therapy (*32,33*), owing to the greatly prolonged residence time of particles in the peritoneal cavity and the obstruction of lymphatic drainage that occurs in ovarian cancer (*34*).

Table 1. Characteristics of typical liposomes

Diameter	0.05 μ m
Captured aqueous volume	1 L/mole
Membrane volume	1 L/mole
Number of particles	10 ¹⁸ /mole
Lipid molecules/vesicle	60 000

Factors That Determine Performance of Liposome Formulations

Intensive study of liposomes as model membranes and as drug carriers has led to a detailed understanding of the biophysics, cell biology, and pharmacology of liposomes, to a degree shared by few other drug delivery systems. The great variety of constituents from which liposomes can be made, as well as the range of methods to prepare and process liposome formulations, has led to the elucidation of many parameters that determine the performance of the dosage form:

1) Liposome *diameter* controls not only the residence time of liposomes in the blood after IV administration (small liposomes circulate longer than large liposomes) but also controls the aqueous volume per particle. For small liposomes (about 0.05 μm), the volume of the interior aqueous compartment is approximately equal to the volume of the hydrocarbon phase of the membrane (Table 1).

2) *Electrostatic charge*, determined by the constituents from which liposomes are formed, modulates not only circulation time but also the interaction of liposomes with cells (uncharged liposomes circulate longer than do charged, but charged liposomes interact more avidly with cells, cf. Fig. 4).

3) *Membrane fluidity* can alter not only stability and permeability of liposomes (35) (gel phase or solid liposomes tend to be more stable in serum and circulate longer in the blood) but also can control the ability to encapsulate hydrophobic drugs within the membrane. Fluid liposomes have more disordered hydrocarbon domains and thus may accommodate bulky lipid-soluble drugs within the membrane to a greater extent. The *phase transition temperature* (T_m) at which liposome membranes melt from the gel to the fluid state also modulates liposome stability. The primary determinants of T_m are the length and degree of saturation of the phospholipid acyl chains, and manipulations of T_m are possible in order to form liposomes that will release their drug contents in response to a particular temperature (e.g., local release with localized hyperthermia).

4) Phospholipid *headgroup hydration* varies with the phospholipids used for liposome preparation. Biophysical investigations have demonstrated that liposomes containing phosphatidylcholine (PC) are less likely, under certain conditions, to aggregate and undergo fusion than are liposomes containing phosphatidylethanolamine (PE) (36). Both PC and PE are electrostatically neutral zwitterions at physiological pH, but the degree of hydration of PE is believed to be somewhat less than that of PC (37). A related phenomenon, *steric stabilization* of liposomes by the inclusion of synthetic or naturally occurring amphiphiles, is achieved by localization of bulky, hydrated groups such as polyethylene glycol, inositol, or complex carbohydrates near the membrane surface (38). Results include an increased stabilization of liposomes in biological fluids and enhanced circulating half-life (26–28).

5) *Other amphipaths* may be included in the liposome membrane. Most often, cholesterol is a constituent be-

cause of its ability to improve liposome physical stability (35). Other amphipaths may be chosen to confer special properties on liposomes, such as the preparation of pH-sensitive liposomes that undergo membrane fusion and release their contents at the mildly acidic pH encountered within endocytic vesicles.

6) *The method of preparation* can be varied to accommodate either the constraints of process scaleup or the requirements of particular agents to be formulated (39); for example, encapsulation of molecules that are chemically or physically unstable may favor one method for liposome preparation over others.

7) *Storage conditions* may alter the properties of liposomes in either innocuous or important ways. For example, lyophilization of liposomes with appropriate cryoprotectants may result in a formulation that undergoes aggregation and fusion on hydration. The generation of larger particles could be disastrous if long-circulating liposomes were desired, or it could be unimportant in a depot preparation that would be deposited at some extravascular site.

Recent Developments in Liposome Technology

Among the most significant recent developments in the liposome field is recent work that shows that several new, effective strategies now exist for controlling liposome distribution in vivo. Addition of gangliosides, polyethylene glycol- or inositol-containing phospholipids (26–28), results in a nominal fourfold increase in liposome circulating half-life. Delayed clearance allows greater access of liposomes to the extravascular interior of model tumors after intravenous liposome administration (40).

RESULTS AND DISCUSSION

Prototype Taxol-Phospholipid Formulations

To test the hypothesis that liposomes may be suitable carriers for Taxol, a systematic investigation of variables outlined above was undertaken in order to develop prototype Taxol-liposome formulations. The main constraint placed on formulations was that they be of sufficient stability and Taxol content to allow testing of cytostatic activity in vitro and antitumor activity and toxicity in vivo. Taxol content of liposomes and Taxol:lipid ratio was determined both before and after separation of phospholipid from unincorporated Taxol. Liposome concentration was determined by phosphorous assay (41), and Taxol was determined by chromatography (42). The physical state of the formulation was evaluated using differential interference contrast microscopy (DIC), in order to detect liposome aggregation or fusion, and precipitation of Taxol.

Physical stability of the liposomes varied as the method of preparation and lipid content was varied (Fig. 1). In each panel, the concentration of phospholipid and drug was the same. Fig. 1A shows a preparation of Taxol liposomes postprocessed to produce particles in the ap-

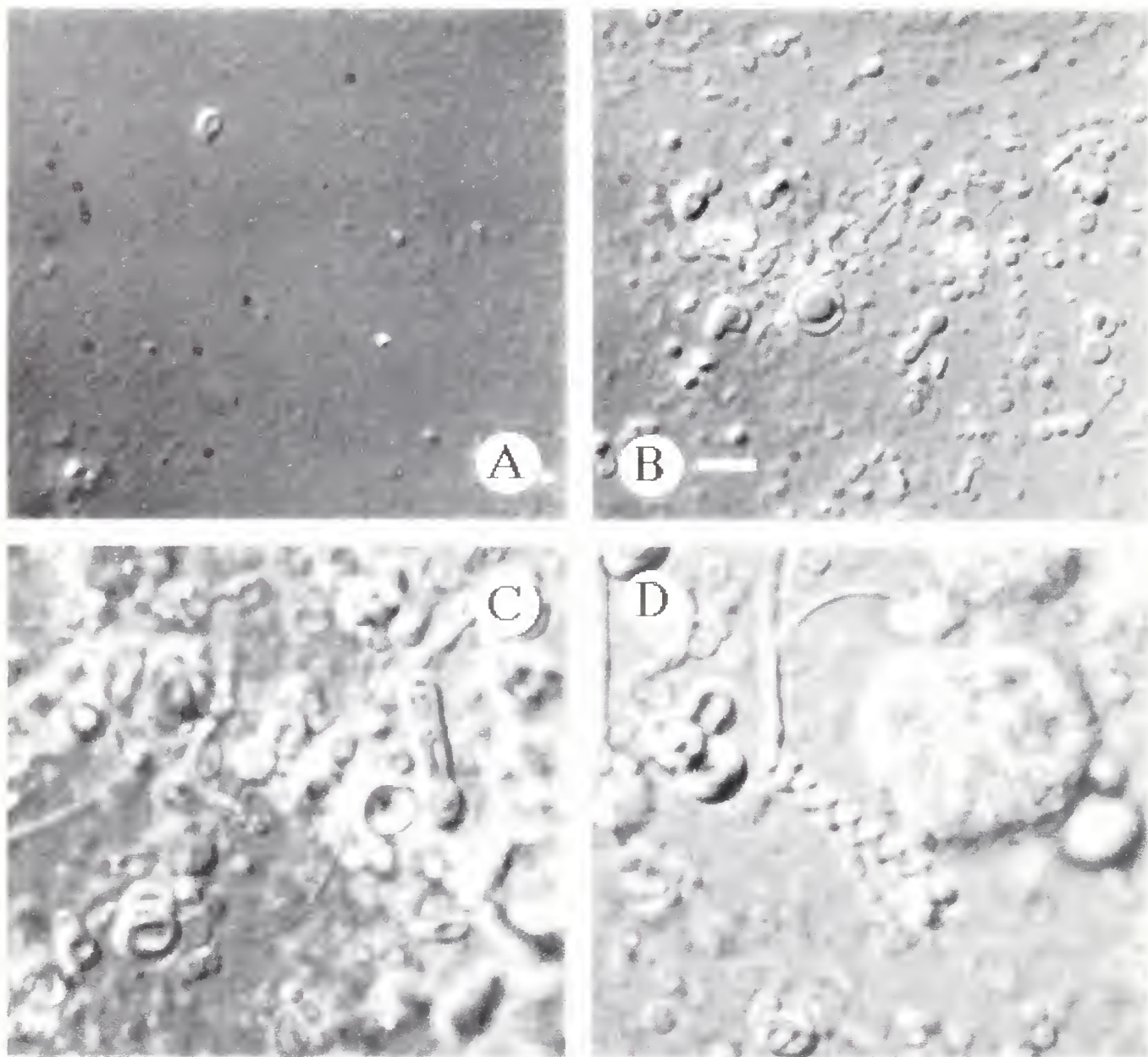


Fig. 1. Morphology of Taxol-liposome formulations. Taxol was incorporated into liposomes and examined by DIC microscopy. In all images, the phospholipid concentration was 30 mM, and the Taxol:phospholipid ratio was held constant. Only the specific lipid constituents, the method of liposome formation, and the postprocessing steps were varied. A, Liposomes postprocessed to $<0.1 \mu\text{m}$ diameter. B, Formulation consisting of large uni- and oligolamellar liposomes. C, Formulation consisting of heterogeneous, multilamellar liposomes. D, Formulation consisting of lipid/Taxol complexes of varying morphology, along with precipitated, Taxol-rich structures. Bar = $2 \mu\text{m}$.

proximate size range of $0.08 \mu\text{m}$. Most particles are below the limit of resolution of optical microscopy. Fig. 1B shows liposomes of similar composition, except that both small and large oligo- and unilamellar liposomes were produced. Altering phospholipid composition produced particles of greater size and more variable morphology (Fig. 1C). In Fig. 1D, a formulation contains both helical strands of membrane and precipitated Taxol:lipid aggregates.

Further systematic variation of the initial Taxol:lipid ratio and the liposome phospholipid and lipid constituents led to a series of metastable formulations (Fig. 2). These formulations showed quantitative incorporation of drug and good short-term stability. Fig. 2A shows a formulation of predominantly small ($<0.1 \mu\text{m}$) liposomes shortly after preparation. After storage for 3 days (Fig. 2B), crystals of Taxol appeared in the aqueous medium, and the Taxol content of the particles decreased concomi-

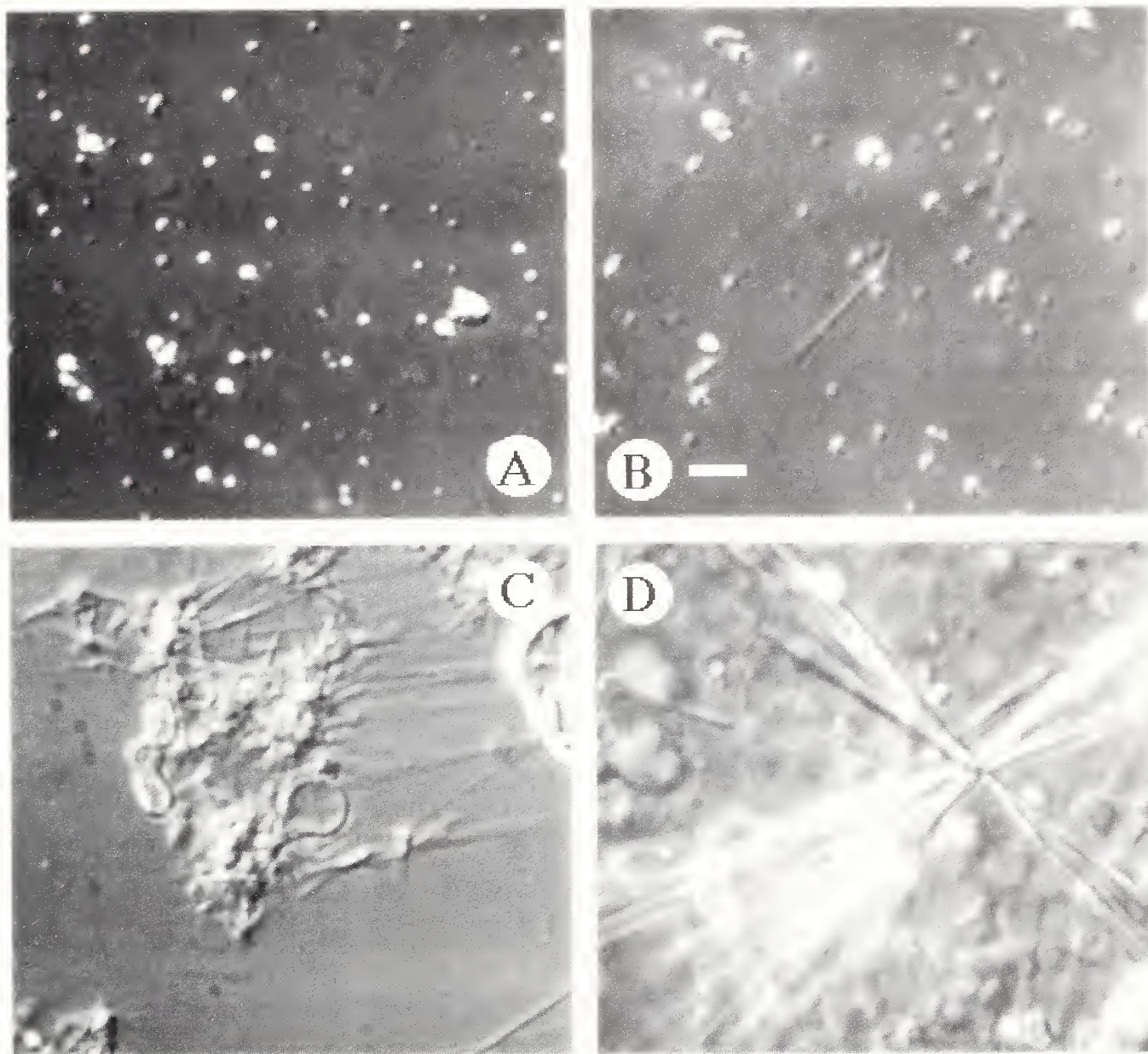


Fig. 2. Morphology of metastable Taxol-liposome formulations. Taxol was incorporated into liposomes and examined by DIC microscopy as in Fig. 1. In all images, the phospholipid concentration was 30 mM, and the Taxol:phospholipid ratio was held constant. Only the specific lipid constituents and the postprocessing steps were varied. A, Liposomes postprocessed to $<0.1 \mu\text{m}$ diameter, shown immediately after preparation. B, The same formulation as in (A), after 3 days' storage at 4°C . Note presence of single Taxol needle. C, Formulation (after 3 days' storage at 4°C) of different composition from (A), in which Taxol needles appear in conjunction with aggregated liposomes and lipid complexes. D, Formulation (after 2 days' storage at 4°C) in which large Taxol crystals emanate from central, possibly lipid-rich particle. Bar = $2 \mu\text{m}$.

tantly, as reflected in the Taxol:phospholipid ratio (data not shown). The morphology of Taxol crystals varied for different metastable Taxol-liposome formulations, suggesting significant interaction of certain lipids with Taxol. In some cases, single, apparently free-floating Taxol needles were produced (Fig. 2B). In others, needles were intimately associated with liposomelike structures (Fig. 2C) or appeared to be organized around a nucleus of lipid

(Fig. 2D).

Cytostatic Activity of Prototype Taxol Liposomes

From our studies of the physical stability, drug:lipid ratio, and chemical stability of Taxol-lipid formulations, boundary parameters for Taxol liposomes were established, and a series of prototype liposomes were selected

for further investigation. One formulation investigated consisted of small ($\sim 0.1 \mu\text{m}$) particles of relatively low electrostatic charge. Physical stability at 4°C exceeded 1 week, allowing evaluation of formulation efficacy. Cytostatic activity was compared with that of free Taxol for a variety of tumor cell lines that will be of interest in future *in vivo* experiments (Fig. 3). For the cell lines chosen, the sensitivity to free Taxol varies nearly 100-fold. Colon-26, a murine model for invasive and recurrent colon cancer (43), showed the lowest sensitivity to Taxol. A rat gliosarcoma, 9L, likewise was relatively resistant to Taxol. A121a, a human ovarian tumor cell line established prior to treatment (44), was the most sensitive, and growth inhibition occurred at concentrations 100-fold lower than that required to inhibit growth of Colon-26. Other human ovarian tumor cell lines (Hey-1b and A90) showed intermediate sensitivity.

The sensitivity of cells to free Taxol also varied with the experimental design (Fig. 3). In one protocol, Taxol was dissolved in dimethylsulfoxide (DMSO) and diluted into tissue culture dishes to 0.5%–1.0%, a concentration at which DMSO had a minimal effect on cell growth. A second approach was to resuspend dry Taxol directly in serum-containing cell growth medium, filter to remove undissolved drug, and verify the Taxol concentration chromatographically after extraction (45). For most cell lines, free Taxol showed similar growth-inhibitory effect, regardless of the method by which the drug was solubilized. However, in other cell lines (e.g., 9L rat gliosarcoma and A90 human ovarian tumor, Fig. 3), DMSO enhanced Taxol activity. Because all experimental results were corrected for any effect of DMSO on cell growth, the significant enhancement of Taxol activity may have a mechanistic basis, such as increased drug uptake, reduced drug efflux, or other effect.

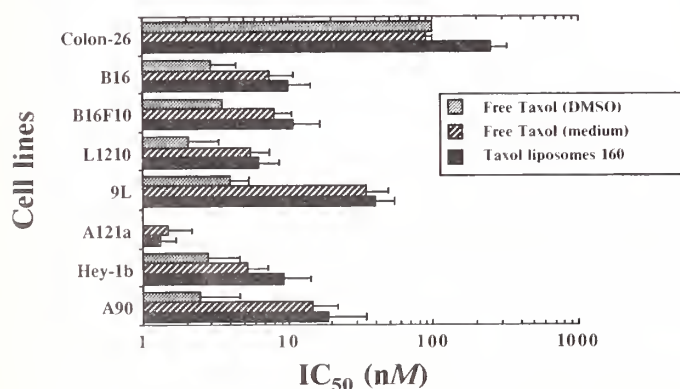


Fig. 3. Growth-inhibitory properties of Taxol liposomes. Cells were plated at a density of $2 \times 10^4/\text{mL}$ in multiwell plates and allowed to adhere overnight. Triplicate wells were exposed to various concentrations of Taxol, added either as liposomes (solid bar) or as a 100 \times concentrated stock in DMSO (stippled bar), or absorbed to serum proteins (hatched bar) in the absence of organic solvent. Cells were enumerated after 72 hours, and the IC_{50} (50% growth inhibition) value for each concentration-effect curve was calculated graphically. Experiments were repeated at least twice. Cell lines are as follows: Colon-26, murine colon carcinoma; B16, murine melanoma; B16F10, highly metastatic variant of B16 murine melanoma; L1210, murine leukemia; 9L, rat gliosarcoma; A121a, Hey-1b, and A90, human ovarian tumor cell lines.

In most cases, the Taxol-liposome formulation was equipotent to free Taxol. In other cases (e.g., Colon-26), liposomes were slightly, but reproducibly, less potent than free Taxol. Because the Taxol content of liposomes was determined chromatographically, chemical instability of Taxol was ruled out. Therefore, we evaluated the degree to which liposomes of similar composition interact with Colon-26 cells by encapsulating phosphonacetyl-L-aspartate (PALA) as a probe for cellular delivery. The cytostatic activity of PALA-containing liposomes requires endocytosis of liposomes by cells (46). Fig. 4 shows the dependence of PALA cytostatic activity, relative to the activity of free PALA, as a function of the liposome negative charge. With 50 mol% or less negatively charged phospholipid in the formulation, PALA liposomes are less- or equipotent to free drug. Highly charged liposomes are the most potent, because negative charge mediates more avid endocytosis of liposomes. With 10 mol% negative charge, PALA liposomes are less potent than free drug, suggesting that highly stable liposomes sequester the drug in the external medium, do not interact significantly with cells, and therefore do not deliver the drug to the cell interior.

Similar experiments with two additional cell lines are included for comparison and illustrate both the magnitude by which the appropriate liposome electrostatic charge can enhance drug delivery to cells and the variation in the fraction of negative charge required to achieve maximal

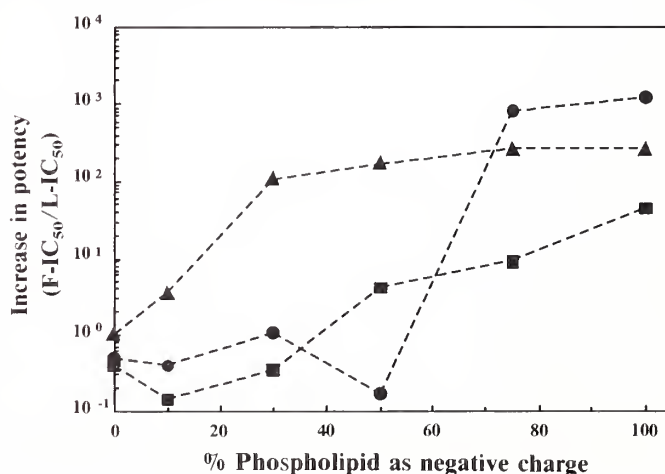


Fig. 4. Modulation of liposome-mediated delivery by liposome electrostatic charge. Cells were plated for growth-inhibition experiments as in Fig. 3 except that liposomes contained PALA encapsulated at 35 mM, as a probe for cellular delivery. Liposomes were composed of distearoylphosphatidylcholine (DSPC), distearoylphosphatidylglycerol (PG), and cholesterol. The phospholipid:cholesterol ratio was kept constant at 2:1, but the PG:DSPC ratio was varied from 0:100 ("0% negative charge") to 100:0 ("100% negative charge"). Triplicate wells were exposed to various concentrations of free PALA or encapsulated PALA, and cells were enumerated after 72 hours. The IC_{50} value for each concentration-effect curve was calculated graphically. All experimental points were determined in triplicate, and experiments were repeated at least three times. Potency was calculated as the ratio of the IC_{50} for free PALA relative to PALA-containing liposomes. For most points, the standard deviation is smaller than the symbols used in the figure. Squares: Colon-26 cells. Triangles: CV-1 African Green Monkey kidney epithelial cells; Circles: J774 murine macrophagelike tumor cells.

liposome-mediated delivery (Fig. 4). CV-1, an epithelial cell line from African Green Monkey kidney, shows maximal enhancement of PALA liposome potency (200-fold) with 30 mol% or more negative charge. In contrast, J774 murine macrophage tumor cells show little enhancement of PALA delivery with 50 mol% or less negative charge, but maximal potency (1200-fold) is observed with 75 mol% or more charge. Thus cells vary in the liposome surface charge density required for avid endocytosis.

The prototype Taxol-liposome formulation tested for cytostatic activity in Fig. 3 consisted of less than 50 mol% negative charge. We hypothesize that the lower activity of Taxol liposomes on Colon-26 tumor cells, compared with free drug, may result from the fact that liposome-cell interaction is not optimal. Higher electrostatic charge could promote liposome-cell interaction and thereby enhance cellular delivery. For certain applications, such as direct administration to the tumor-containing site [e.g., intraperitoneal (IP) administration in ovarian cancer], highly negatively charged liposomes may be of benefit. However, because the prototype formulation developed here was chosen for intravenous delivery to a subcutaneous (SC) tumor, negative charge was reduced to promote longer circulation time in the blood.

Toxicity of Prototype Taxol Liposomes In Vivo

As a prelude to therapeutic experiments in animal tumor models, Taxol-liposome formulations were tested to determine the maximum tolerated dose (MTD) in healthy mice. In our hands, mice tolerated ~50 mg/kg of free Taxol by the IP route and ~30 mg/kg by the IV route. The liposome formulation designated NN (Table 2) apparently was better tolerated than free Taxol in Cremophor EL, because the MTD exceeded 200 mg/kg. Surprisingly, the formulation was lethal by the IV route. Subsequent investigation revealed that the formulation, although stable under conditions used for in vitro assay, was metastable under conditions used for animal experiments. In vitro evaluation procedures were amended to identify metastable formulations with the peculiar properties of formulation NN. An extensive reformulation effort was undertaken, which yielded a stable Taxol-liposome preparation (#165). Formulation 165 consisted of small (<0.1 μ m) liposomes having relatively little electrostatic charge. Stability at 4°C exceeded 1 week, a nominal constraint applied to prototype formulations. In vitro cytostatic ac-

tivity for a similar formulation is presented in Fig. 3. By both IV and IP routes, the formulation was well tolerated, with an MTD exceeding that of free Taxol. It was necessary to fractionate the dose given by IV administration, owing to the large volume of liposomes required for the 200 mg/kg dose.

Antitumor Activity of Prototype Taxol Liposomes

Colon-26, the murine tumor line identified as Taxol-resistant in in vitro experiments (Fig. 3), was chosen as the initial target investigated in therapeutic experiments. Tumors were implanted SC, and treatment was initiated on

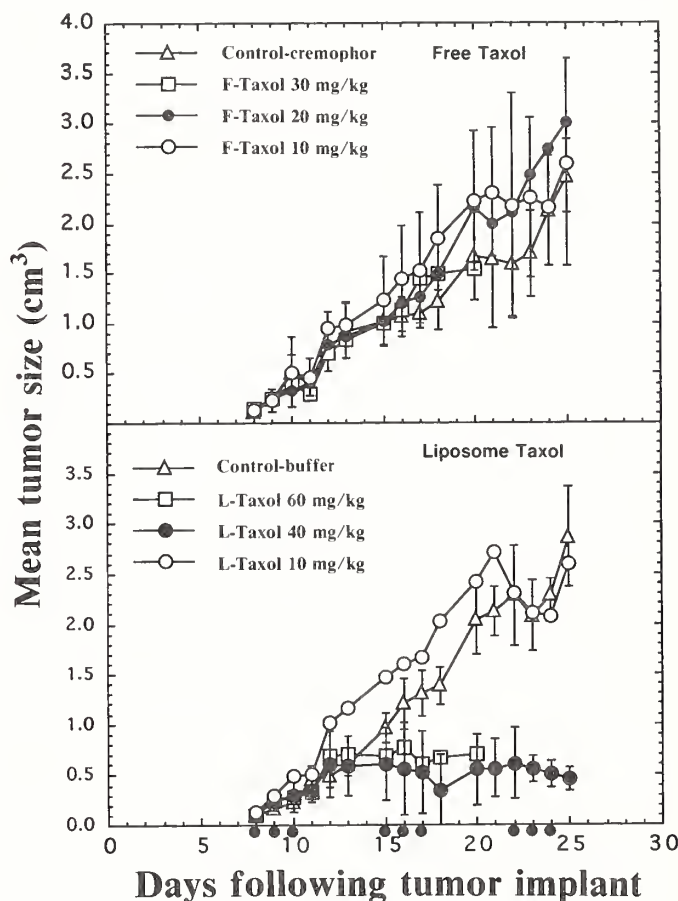


Fig. 5. Antitumor efficacy of prototype Taxol liposomes in Colon-26 murine model. Colon-26 tumor cells (10^6 cells in 0.2 mL) were implanted SC on the right flank of 16 to 20 g Balb/c female mice. Eight days after implantation, when the tumor was measurable, treatment with free Taxol or Taxol liposomes was begun. Treatment consisted of doses of 10, 20, or 30 mg/kg free Taxol in Cremophor EL, diluted 1:3 with saline and administered at a concentration of 2 mg/mL (top panel). Alternatively, Taxol liposomes in saline, at a concentration of 3 mg/mL Taxol, were used to give doses of 10, 40, or 60 mg/kg (bottom panel). Saline and Cremophor EL (diluted 1:3) were used as control treatments. Each treatment group consisted of 10 animals, and symbols represent the mean tumor volume for the group. For clarity, standard deviations are not included for all curves; those shown are for the most important data and are representative. Animals received injections three times weekly, and treatment was given for 3 weeks, as indicated by filled circles along the abscissa. Tumor dimensions along three axes were measured daily, and the tumor volume was calculated. For humane reasons, animals were sacrificed when tumor volume exceeded 3 cm³.

Table 2. Toxicity of Taxol in healthy Balb/c (F) mice: Free and liposome formulations

Formulation	IP route	IV route
Taxol/Cremophor EL		
Single dose	~ 50 mg/kg	~ 30 mg/kg
Taxol/Liposome NN		
Single dose	>200 mg/kg	Lethal
Taxol/Liposome 165		
Single dose	>200 mg/kg	>200 mg/kg*

*In 4 doses over 3 hours.

day 8. Free Taxol in Cremophor EL was tested at 10, 20, and 30 mg/kg per injection. Taxol liposomes were tested at 10, 40, and 60 mg/kg per injection. Animals received injections on 3 successive days of each week, and treatment was given for 3 weeks. Buffer or Cremophor EL without Taxol was used as a control treatment. The results show no detectable delay in tumor progression by any free Taxol dose level (Fig. 5). The highest dose of free Taxol, 30 mg/kg, was lethal to all animals by day 21 (12 days after initiating Taxol treatment). The highest nonlethal free Taxol dose, 20 mg/kg (180 mg/kg in treatment course), was ineffective. In contrast, Taxol liposomes given at 40 mg/kg (360 mg/kg in treatment course) controlled tumor growth. A lower dose, 10 mg/kg, showed slight antitumor effect. The highest dose, 60 mg/kg, was toxic and was lethal to all animals by day 21.

CONCLUSIONS

A systematic approach has been taken to elucidate the major parameters that govern formulation of Taxol in phospholipid suspensions. Prototype formulations have been identified that have sufficient chemical and physical stability to test the hypothesis that liposomes can alter the pharmacology of Taxol, in addition to providing a biologically compatible carrier in which to administer Taxol (47). Testing in vitro against a variety of tumor cell lines demonstrated that Taxol liposomes retain Taxol growth-inhibitory activity. Preliminary results on antitumor efficacy against Colon-26, a Taxol-resistant murine tumor, showed no effect of free Taxol administered in Cremophor EL. In contrast, Taxol liposomes showed a delay of tumor progression at a dose that was higher than the MTD of free Taxol.

Ongoing work seeks to determine the mechanism of increased efficacy shown by Taxol liposomes. Our operant hypothesis is that the primary function of liposomes is to reduce the dose-limiting toxicity of chronic Taxol dosing, thus allowing the administration of greater, tumor-controlling doses. Additional, more Taxol-sensitive tumor models will be investigated, such as human ovarian tumors in athymic nude mice. Because no dose of free Taxol controlled Colon-26 tumor growth, it is not possible to investigate whether antitumor potency of the Taxol-liposome formulation exceeds that of the conventional free Taxol formulation. Tumor models that respond also to free Taxol will allow examination of the impact of formulation on both efficacy and toxicity.

Additional work is required before the prototype formulations developed here can be considered substitutes for the presently used Taxol/Cremophor EL formulation. More extensive characterization and development must be devoted to the Taxol formulation itself; the prototypes in hand likely can be optimized further in terms of both efficacy and stability. Additional necessary work, presently under way, includes efforts to produce Taxol liposomes in a "pharmaceutically rational" manner.

Scaleup of the formulation process will be required to produce the quantities of Taxol liposomes needed for preclinical testing. Finally, more complete investigation will be required to determine whether novel toxicities will be encountered with liposome-based formulations, and antitumor efficacy testing, in a wider range of model systems, must be undertaken to determine the advantages and limitations of these novel Taxol formulations.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

²Taxotere is used in this monograph to refer to the drug that now has the generic name docetaxel and the registered trade name Taxotere® (Rhône-Poulenc-Rorer Pharmaceuticals Inc., Collegeville, Pa.).

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Structure-Activity Relationships of Taxol and Taxotere Analogues

D. Guénard, F. Guéritte-Voegelein, J. Dubois, P. Potier*

From Taxol, Taxotere, and 10-deacetyl baccatin III, a number of compounds have been prepared. Their biological activity was evaluated on microtubule disassembly at 0 °C. The conformation of these Taxol and Taxotere analogues was determined by molecular modeling experiments and nuclear magnetic resonance spectroscopy and compared with the structure of Taxotere in the crystal, obtained by an x-ray analysis. The results of these studies give information on the crucial parts of the active molecules involved in the binding to tubulin. [Monogr Natl Cancer Inst 15:79-82, 1993]

Since the first publication in 1971, describing the isolation of Taxol¹ from the bark of the Pacific yew tree (*1*), a large number of studies on this complex molecule have been developed in both the chemical and biological fields. After the description of its unique mode of action on the tubulin-microtubules system by Susan Horwitz in 1979 (*2*), many analogues have been prepared either from Taxol itself or from 10-deacetyl baccatin III, a natural precursor isolated from the yew leaves (*3*). Among these substances, a new analogue, called Taxotere² (*4*), is becoming a new leader in this series because of its greater potency and its better chemical availability than Taxol (*5-7*) (Fig. 1).

For Taxol and Taxotere analogues, the pharmacological evaluation on microtubule disassembly or on the assembly promotion of tubulin seems to be more sensitive than the cytotoxicity assay, especially for compounds having a weak binding to tubulin, and is consequently more suitable for the study of structure-activity relationships in the taxoid series. The importance of this latter point is underlined by the fact that 10-deacetyl baccatin III, which is devoid of cytotoxicity, was selected on the basis of its slight inhibition of the microtubule disassembly process.

As a part of our program to relate structure and conformation to the antimitotic activity, we prepared a number of Taxol analogues. The most important contribution for the conformational study of active taxoids came from the x-ray analysis of Taxotere (*8*), showing the conformation of the side chain at C-13 in relation to the taxan skeleton as well as the crystal lattice interactions. The structure of Taxotere in the crystal was compared with the conformation of Taxotere, Taxol, and related compounds obtained by nuclear magnetic resonance (NMR) experiments at 400 MHz (quantitative NOESY and ROESY) and molecular modeling studies performed on a Silicon Graphics work station using MacroModel (MM2 as the force field, with and without the presence of water molecules)

(Dubois J. et al., unpublished data). The various conformers differ by the position of the side chain toward the taxan skeleton. According to our results, the difference between the conformer of lowest energy and the following of highest energy is about 1 kcal. Moreover, the energy barrier to obtain the less favored conformations from the lowest one was about 50 kcal.

RESULTS AND DISCUSSION

Comparison of the Solution and Crystal Structure of Taxotere

Nuclear Overhauser effect (NOE, performed in CDCl₃, CD₃OD, or CD₃CN) data on Taxotere showed the closeness of the side-chain hydrogens (H-2', H-3', phenyl at 3') and the methyl groups, Me-18 and 4-acetyl group of the taxan skeleton. The conformer derived from this NMR experiment is virtually identical to the most stable conformer obtained by molecular modeling studies. Similar results from NMR experiments performed on a water-soluble Taxotere analogue (7,10-diglycyl derivative) in D₂O led to the same structure in solution. On the other hand, and despite the close analogy of the x-ray structure of Taxotere and the conformer of lowest energy, there exists a slight difference in the orientation of the side chain with respect to the taxan skeleton (Fig. 2). This difference could be explained by the closeness of nonpolar groups to decrease their interaction with the protic medium. Thus, in the crystal lattice, intermolecular interactions occur between the hydrophobic *tert*-butyl and phenyls groups of neighboring molecules (Fig. 3). On the contrary, the intramolecular proximity of the C-2 aromatic and C-3' *tert*-butyl groups is favored in solution.

Results of Structure-Activity Relationships

Compounds with or without side-chain substituents at C-2' or C-3' in the natural (2'R,3'S) or unnatural configurations have been prepared to determine the influence of each of them on microtubules disassembly (*9*). Similarly to Taxotere, conformer generations have been performed, and the most stable conformers were compared with their structure derived from NMR experiments.

This study allows us to propose several conclusions that are not, today, invalidated by the most recent results obtained with the last analogues assayed in our laboratory or published recently in the literature (*10*). The results, taken as a whole, show that the compounds that have the best activity possess, in solution, a similar conformation

*See "Notes" section following "References."

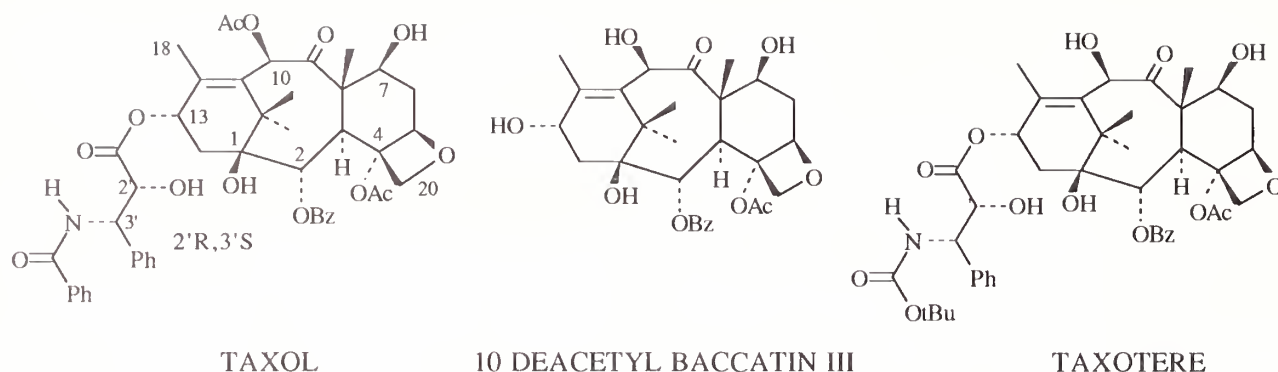


Fig. 1. Reference products in the taxoid series.

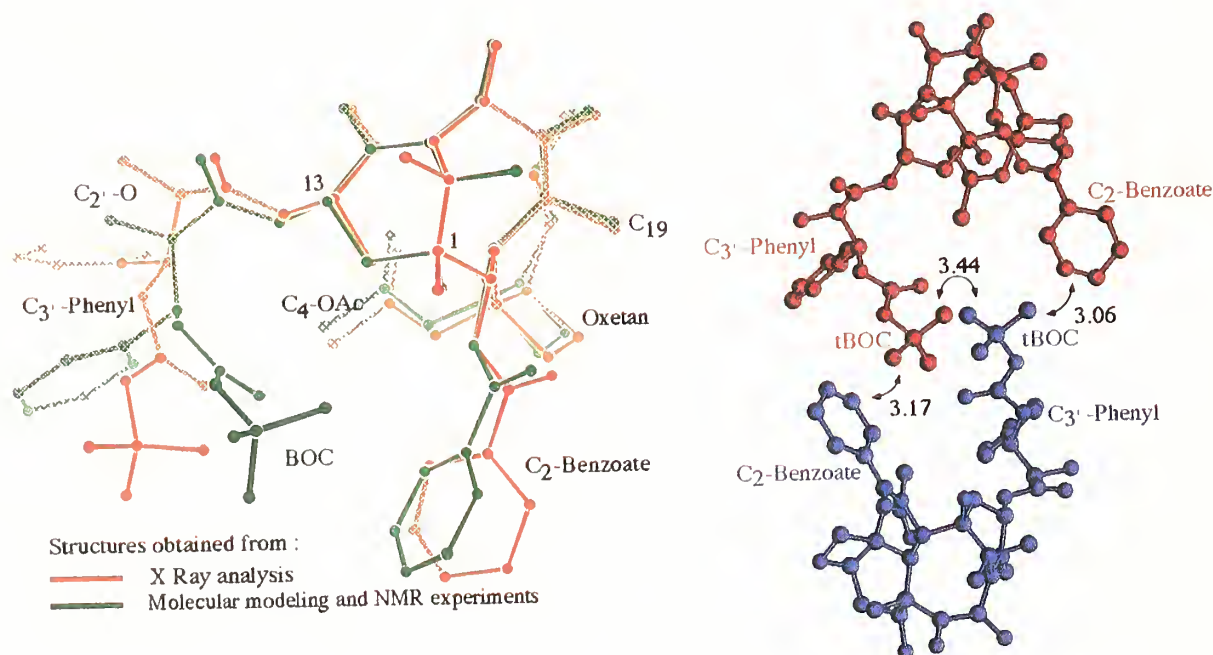


Fig. 2. Comparison between structures obtained from molecular modeling and x-ray studies (minimal interhydrogens distances in Å in the crystal lattice).

to that of Taxotere. Slight variations occur only in the relative position of the side-chain substituents according to the configuration at C-2' and C-3'.

The main conclusion to emerge from these studies is that the interaction of active taxoids to tubulin is quite sensitive to the conformation of the side chain and to the presence of hydrophilic and hydrophobic areas involving both the side chain and the taxan skeleton (Fig. 4). The hydrophilic area involves the hydroxyl groups at C-2', the carbonyl at C-1', and the oxygenated functions at C-7, C-9, and C-10. The second area is hydrophobic in nature and includes the benzoate at C-2 and the substituent of the amide or carbamate at 3'. The side chain exhibits a particular conformation due to intramolecular hydrogen bonding (C₁'=O—2'-OH, on one hand and 2'-OH—NH on the other) and hydrophobic interaction between

the carbamate (or amido) group at C-3' and the benzoate at C-2.

With regard to the structural modifications, it has been shown that the presence of a Taxol-like side chain at C-13 is essential for a good binding to the receptor and that modifications at C-7 and C-10 generally have little effect on the activity (11,12). The presence of the 2' hydroxyl is not essential for strong binding to tubulin. Indeed, 2' deoxy-Taxotere is only sixfold less active than Taxotere. Its presence, however, must stabilize the binding to the protein through a direct interaction with polar peptidic residue. This hypothesis is verified by the fact that ester derivatives at C-2', which possess a conformation similar to that of Taxotere, have a weak affinity for tubulin.

The phenyl group at 3' has little effect on the side-chain conformation; it probably has a stabilizing effect in the

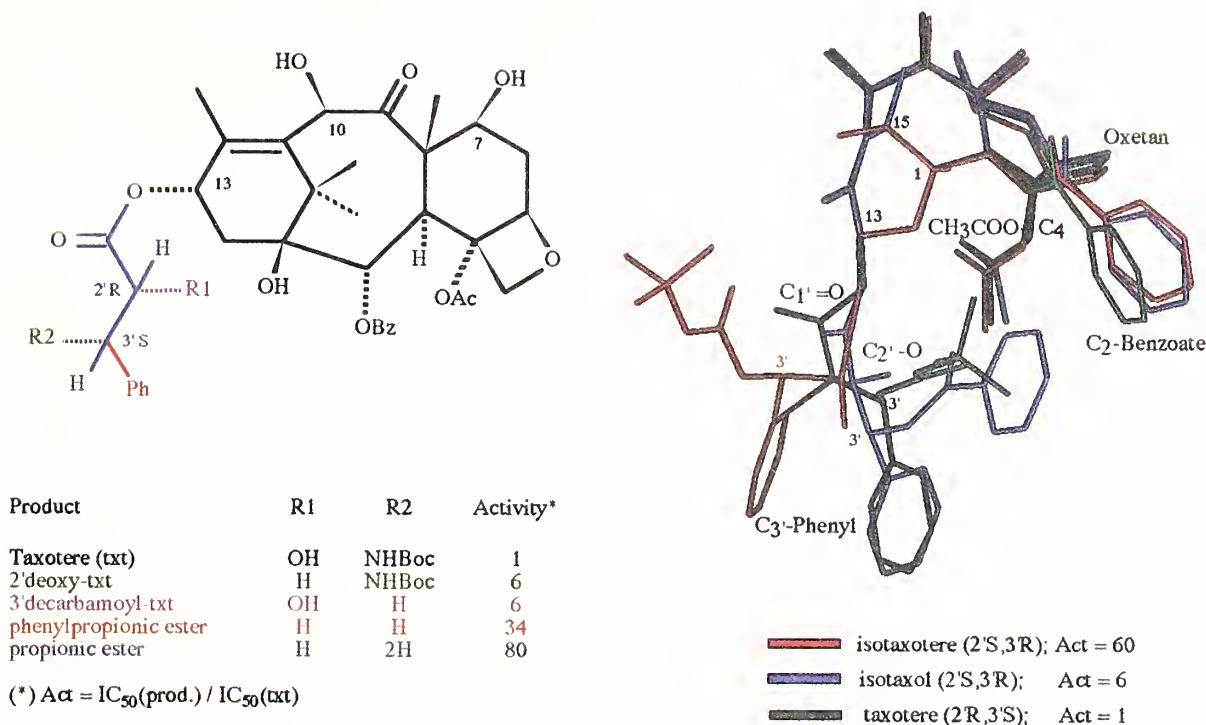


Fig. 3. Main structure-activity relationships in the Taxotere family. Comparison of active and inactive conformations.

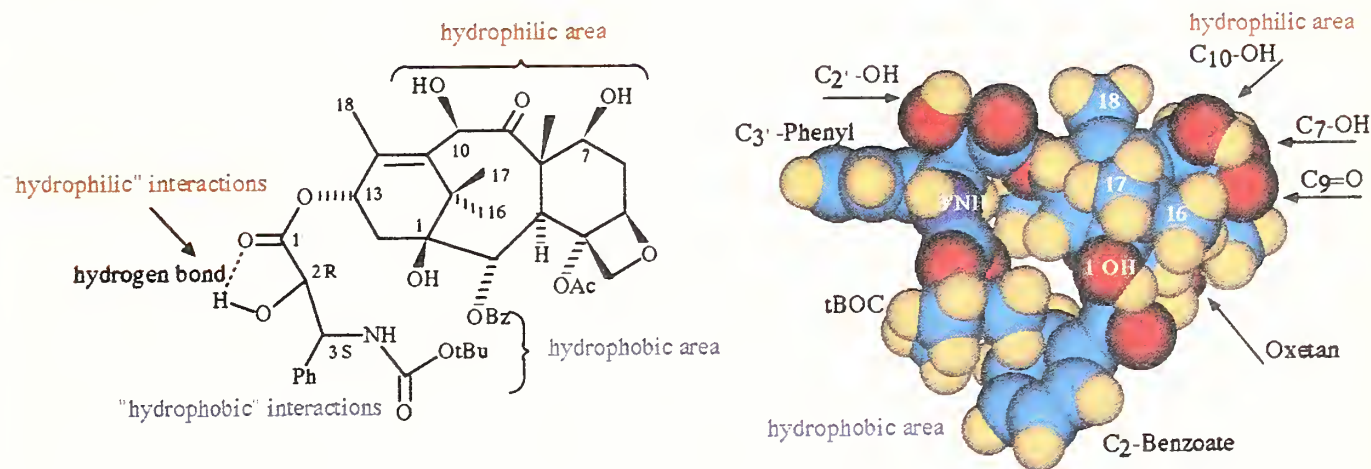


Fig. 4. Main areas on the Taxotere molecule.

drug protein interaction, and its replacement by a methyl group strongly reduces the binding to tubulin (13,14). Hydroxyl substitutions of the phenyl group in the para position do not seem to affect the activity (15).

Concerning the 3' amido group, its substitution by other hydrophobic N-acyl groups does not decrease the activity. This group is located under the "umbrella" of the 2-benzoate. This part of the molecule is close to a hydrophobic site of tubulin. Bulky functionalities, such as fluorescent probes, can be added at this position without loss of affinity to the Taxol-binding site.

If it is hypothesized, as the conformational study of analogues showed, that the "active" conformation is represented by the structure of Taxotere, it should be noticed that the gain in activity between an analogue without any substitution at 2' and 3' and Taxotere is the product of the separate contributions brought by the substituents at carbons 2' and 3'.

To date, it is difficult to know the exact contribution of the oxetan ring to activity because most of the synthetic compounds bearing a cleaved oxetan possess other structural modifications (inversion of the C-5 substituent, re-

moval of the acetyl at C-4) (16,17). It should also be noted that the lack of the acetyl group induces a slight conformational change of the A ring leading to the modification of the side-chain position.

CONCLUSION

From these studies, we suggest that, in the binding process to tubulin, Taxol-like compounds are recognized by the hydrophobic areas of the taxan skeleton involving the benzoate at C-2. The proximity between this group and the amido (or carbamate) group at C-3' leads to a definite orientation of the other functionalities of the side chain. Thus, specific interactions between tubulin and the 3' phenyl and 2' hydroxyl groups could stabilize the fixation. On the contrary, the hydrophilic area, including functions at C-7,9,10, may remain outside the binding site, in the biophase. Concerning the in vitro cytotoxic activities, a generally good correlation with the tubulin assay has been noted, confirming the effectiveness of this primary assay.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

²Taxotere is used in this monograph to refer to the drug that now has the generic name docetaxel and the registered trade name Taxotere® (Rhône-Poulenc Rorer Pharmaceuticals Inc., Collegeville, Pa.).

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Taxol Effect on Cisplatin Sensitivity and Cisplatin Cellular Accumulation in Human Ovarian Cancer Cells

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Taxol and cisplatin are the two most effective agents discovered to date for treating advanced-stage cancer of the ovary. Learning how best to combine these agents is the focus of preclinical and clinical studies conducted at a number of institutions. Taxol's effect on cellular sensitivity to cisplatin was studied in paired cisplatin-sensitive A2780 and cisplatin-resistant A2780/CP70 human ovarian cancer cell lines. Cisplatin growth curves were generated under conditions of specific sequencing with Taxol, and IC_{50} s (concentrations at which growth is inhibited to 50% of control) for cisplatin were obtained and compared. Taxol was used at an IC_{10} dose in all experiments. Taxol treatments were for 24 hours and cisplatin treatments were for 1 hour in all experiments. Dimethyl sulfoxide (DMSO) was the diluent for all Taxol stock solutions. Separately, the effects of Taxol and DMSO on cisplatin cellular accumulation were measured. End points reported include measures of cytotoxicity and Taxol effects on cisplatin cellular accumulation. Using a microculture tetrazolium assay, cisplatin growth curves were obtained under the influence of Taxol, at a Taxol dose of 3 nM for both cell lines. DMSO alone had no effect on tumor cell growth. In A2780 cells, the influence of Taxol on cisplatin cytotoxicity was modest, whereas cisplatin-induced cell kill was augmented 1.5-fold when cisplatin was given immediately after Taxol. In A2780/CP70 cells, Taxol augmented cisplatin-induced cell kill by 30-fold when cisplatin was given immediately after Taxol; 75-fold when cisplatin was given 24 hours after completion of Taxol; and 19-fold when cisplatin was given 48 hours after completion of Taxol. In separate experiments, neither Taxol nor DMSO alone had significant effects on cisplatin drug accumulation in the cell lines at the Taxol and DMSO doses used. Taxol and cisplatin treatments result in supra-additive cell kill in cisplatin-resistant human ovarian cancer cells, when appropriately sequenced. Cisplatin-induced cell kill in cisplatin-sensitive cells is only modestly affected by Taxol. Thus, the influence of Taxol on cisplatin cytotoxicity is greatest in cisplatin-resistant cells. These studies suggest that in the treatment of ovarian cancer, one should consider administering Taxol before a bifunctional DNA damaging agent when such drug combinations are used. [Monogr Natl Cancer Inst 15:83-88, 1993]

The use of Taxol¹ in combination with other anticancer agents is a topic of intense general interest in medical

oncology. Citardi and colleagues reported that in murine L1210 cells, Taxol and cisplatin treatments resulted in supra-additive cell kill when these two agents were appropriately sequenced (1). Their report suggested that when Taxol is given first, an enhancement in cytotoxicity is seen; whereas when cisplatin is given first, an enhancement in cytotoxicity is not seen. The clinical implications of this observation were immediately obvious because Taxol's activity as a single agent was becoming apparent in a number of human malignancies such as cancer of the ovary (2), breast cancer (3), lung cancer (4), and others. As with all new anticancer agents, after the demonstration of single-agent activity, the next important area of study is the drug's use in combination with other established compounds.

Rowinsky et al. conducted a phase I clinical trial of Taxol and cisplatin, alternating the sequence of the two drugs (5). They reported that the sequence of Taxol followed by cisplatin was associated with less neutropenia, compared to the alternative sequence, which was associated with more profound myelosuppression (5). Whereas cisplatin appeared to affect the pharmacology of Taxol, it was not possible to determine whether there was definitive clinical benefit of one sequence over the other. Because such possible benefit (if it exists) would require clinical phase III studies in more homogeneous patient populations, we felt that *in vitro* studies were warranted to ascertain whether the original observation in L1210 cells was applicable to other cell types.

We have therefore conducted a series of studies to assess the effect of Taxol and cisplatin sequencing on the cytotoxicity of human ovarian cancer cells. For this work, we selected the cisplatin-sensitive A2780 and cisplatin-resistant A2780/CP70 cell lines, which were provided by Dr. Robert Ozols and colleagues (6). For these human ovarian cancer cell lines, there are established data regarding their cisplatin-DNA adduct repair capability (7). Herein we describe our results regarding Taxol's effect on cisplatin-induced cell kill and cisplatin cellular accumulation.

MATERIALS AND METHODS

Cell Growth and Cytotoxicity Studies

Human ovarian cancer A2780 and A2780/CP70 cells were cultured in monolayer using RPMI 1640 media supplemented with 10% fetal calf serum, 2 mM L-glutamine,

*See "Notes" section following "References."

0.2 U/mL insulin, 100 U/mL penicillin, 100 μ g/mL streptomycin (GIBCO, Grand Island, N.Y.). Cells were grown in a humidified chamber containing a mixture of 5% CO₂ and ambient air at 37 °C.

Sensitivity of the cell lines to Taxol was assessed by microculture tetrazolium (MTT) assay, as described by Alley et al. (7). Cells were plated at 1000 cells per well in 96-well plates, and Taxol drug exposure was made the following day. Taxol drug treatments were for 24 hours. Taxol was initially dissolved in dimethyl sulfoxide (DMSO) at 100 μ g/100 μ L (1.171 mM Taxol), and dilutions from this solution were made in media to obtain the drug treatment concentrations of 1 nM, 3 nM, 5 nM, 7 nM, and 10 nM. These Taxol drug doses contained corresponding DMSO concentrations of 12 μ M, 36 μ M, 60 μ M, 84 μ M, and 120 μ M, respectively, which were used to treat control cells labeled as "DMSO controls." After 24-hour Taxol drug treatments, cells were washed twice with phosphate-buffered saline (PBS), treated with fresh drug-free media, and incubated for 5 days. On day 5, after drug treatment, 50 μ L of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (400 mg in 200 mL of PBS) were added to each well and incubated for 4 hours at 37 °C. Analyses of optical density readings were performed using the VV Deltasoft program on a Macintosh computer (Apple, Inc., Palo Alto, Calif.), and percentage cell growth values were obtained.

Sensitivity to cisplatin was also assessed by MTT assay. Cisplatin was initially dissolved in PBS without Ca⁺⁺ or Mg⁺⁺ at 1.0 mg/mL, and dilutions from this solution were made in media to obtain the desired drug treatment concentrations. For A2780 cells, the cisplatin dose range was 0 μ M, 1 μ M, 5 μ M, 10 μ M, 20 μ M, 40 μ M, 80 μ M, and 100 μ M. The drug dose range for A2780/CP70 cells was 0 μ M, 1 μ M, 10 μ M, 40 μ M, 100 μ M, 200 μ M, and 300 μ M. Cisplatin treatments were for 1 hour. After drug treatments, cells were washed twice with PBS, given fresh drug-free media, and incubated for 5 days. On day 5, after drug treatment, MTT assays were performed and plates were analyzed as described above.

Taxol-Cisplatin Sequences Studied

Sequence-dependent supra-additive effects of cisplatin and Taxol have been reported in murine leukemia L1210 cells (1). We examined this sequence-dependent effect in A2780 and A2780/CP70 human ovarian cancer cell lines, using the Taxol-cisplatin drug sequences listed in Table 1. The influence of Taxol on cisplatin cytotoxicity was assessed using MTT assays. Cells were plated at 1000 cells per well in 96-well plates, incubated overnight, and treated the following day with an IC₁₀ (concentration at which growth is inhibited to 90% of control) dose of 3 nM Taxol for 24 hours. Then cells were gently washed twice with PBS and treated with a range of cisplatin doses for 1 hour as listed above. In other experiments, cells were incubated in drug-free media for 24, 48, or 72 hours and then treated with cisplatin (sequences B through E in Table 1). After cisplatin drug treatments, cells were washed with PBS and allowed to grow in drug-free media for 5 days.

In separate experiments, cells were plated at 1000 cells per well in 96-well plates, incubated overnight, and treated the following day with a range of cisplatin doses for 1 hour, followed immediately by 3 nM for 24 hours (sequence F; C>T, Table 1); or cells were treated with cisplatin plus Taxol for 1 hour followed immediately by Taxol for 23 hours (sequence G; C + T>T, Table 1). After drug treatments, cells were washed with PBS and allowed to grow in drug-free media for 5 days. MTT assays were performed, and the percentage of cell growth was obtained and compared to the percentage of growth of cells treated for 1 hour with cisplatin alone (sequence A in Table 1).

Taxol Effect on Cellular Cisplatin Accumulation

A2780 and A2780/CP70 cell lines were grown to 60 to 70% confluence and treated with 3 nM (IC₁₀) Taxol or 36 μ M DMSO for 24 hours, after which A2780 cells were exposed to 18 μ M cisplatin, and A2780/CP70 cells were exposed to 200 μ M cisplatin for 1 hour for the purpose of measuring cellular drug accumulation. Cells were harvested at "0 time" (immediately before cisplatin drug exposure), 15, 30, 45, and 60 minutes during the 1-hour drug exposure. After designated times of exposure to cisplatin, cells were immediately harvested, counted, and "wet-ashed" according to the method of McGahan and Tyczkowska (9). Total cellular platinum was measured using a Perkin-Elmer Model Zeeman/3030 atomic absorption spectrometer with background correction (Perkin-Elmer Corp., Rockville, Md.). Total cellular accumulation of cisplatin was assessed as both nanograms of platinum per million cells (ng Pt/10⁶ cells) and as the percentage of maximal drug accumulation. A value of 100% was assigned to the cisplatin drug level achieved at the end of a 1-hour drug treatment. All other values were expressed relative to the 100% control value.

RESULTS

Cellular Sensitivity to Taxol

In Fig. 1, the sensitivity profiles of human ovarian cancer A2780 and A2780/CP70 cells to Taxol (Fig. 1A)

Table 1. Drug Treatment Sequences for Taxol and Cisplatin

- (A) Cisplatin alone for 1 hr (CDDP, control experiment)
- (B) Taxol for 24 hrs; followed immediately by cisplatin (T>C)
- (C) Taxol 24 hrs; media for 24 hrs; then cisplatin for 1 hr (T>24>C)
- (D) Taxol 24 hrs; media for 48 hrs; then cisplatin for 1 hr (T>48>C)
- (E) Taxol 24 hrs; media for 72 hrs; then cisplatin for 1 hr (T>72>C)
- (F) Cisplatin for 1 hr; followed immediately by Taxol for 24 hrs (C>T)
- (G) Cisplatin plus Taxol for 1 hr; followed immediately by Taxol for 23 hrs (C + T>T)
- (H) Dimethyl sulfoxide alone for 24 hrs; then cisplatin for 1 hr (DMSO, control experiment)

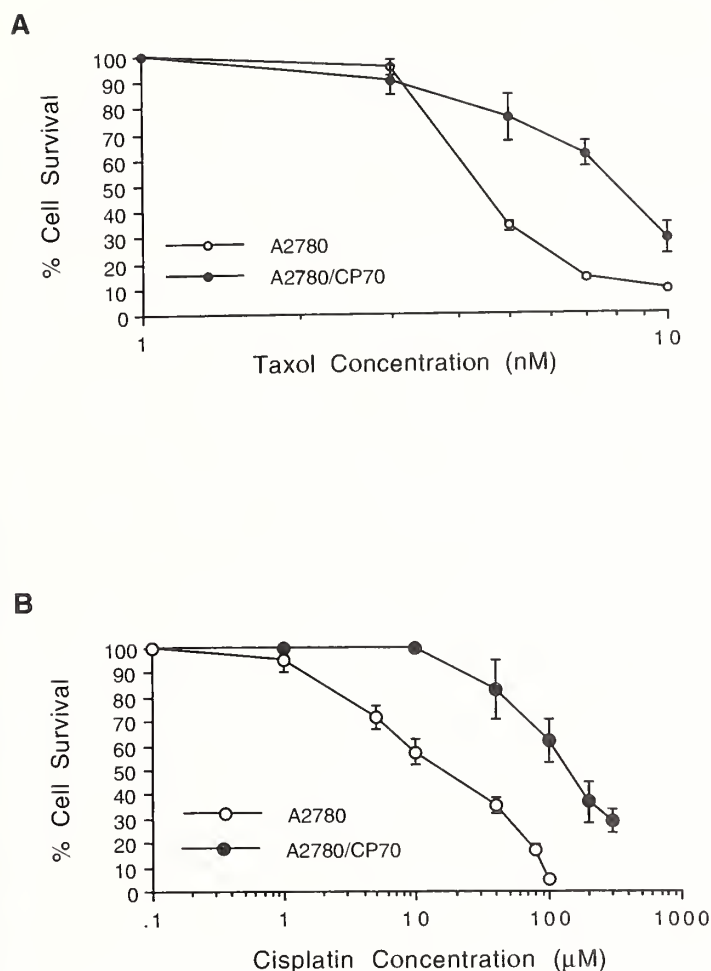


Fig. 1. Sensitivity of human ovarian cancer A2780 and A2780/CP70 cell lines to Taxol (Fig. 1A) and to cisplatin (Fig. 1B). Cells were exposed to various concentrations of Taxol for 24 hours and to various concentrations of cisplatin for 1 hour, as described in "Materials and Methods." Cell survival was assessed by MTT assay.

and to cisplatin (Fig. 1B) are shown. The Taxol sensitivity profile for A2780 cells (Fig. 1A), after 24 hours of exposure to various Taxol drug doses, shows that the concentration at which 10% cell kill (90% survival) occurred (IC_{10}) was 3 nM and 50% cell kill (IC_{50}) was at 4.5 nM. In A2780/CP70 cells, the IC_{10} was 3 nM and the IC_{50} was at 8 nM. DMSO treatment up to a concentration of 120 μ M had no effect on cell kill (data not shown).

The relative sensitivities of these two cell lines to cisplatin are shown in Fig. 1B. As assessed by MTT assay, after a 1-hour exposure to various cisplatin drug doses, the IC_{50} was at 18 μ M in the A2780 cell line. In the A2780/CP70 cell line, 50% cell kill was at 150 μ M. In

comparing the drug exposures associated with 50% cell kill, the A2780/CP70 cell line is eightfold more resistant to cisplatin than the A2780 cell line.

Effect of Taxol on Cisplatin Cytotoxicity

We examined the effect of Taxol and cisplatin sequencing on cisplatin sensitivity in A2780 and A2780/CP70 cells. The sequence-dependent effect of Taxol on cisplatin sensitivity is shown in Fig. 2. For A2780 cells (Fig. 2A), the IC_{50} of cisplatin (CDDP) is 18 μ M as measured by MTT. When cells were treated with 3 nM (IC_{10}) of Taxol for 24 hours, followed immediately by exposure to a range of cisplatin doses ($T>C$), the IC_{50} dose of cisplatin was reduced to 12 μ M. When cells were exposed to cisplatin first ($C>T$), the IC_{50} is 14 μ M. When cisplatin and Taxol were given together, followed by Taxol ($C+T>T$), the IC_{50} dose was 12 μ M cisplatin.

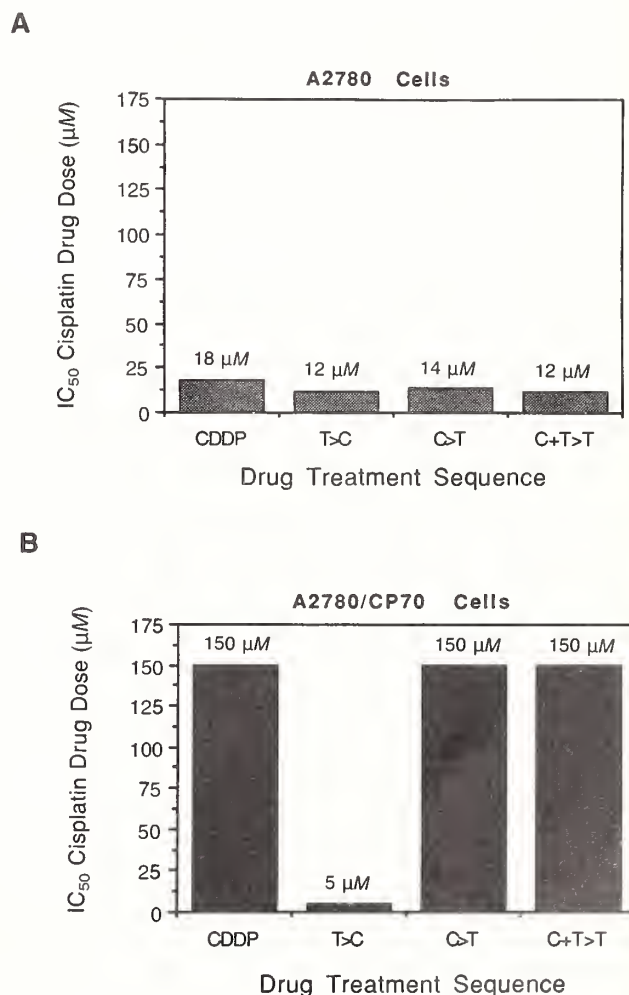


Fig. 2. Effect of Taxol:cisplatin drug sequences on cisplatin cytotoxicity in A2780 (Fig. 2A) and A2780/CP70 (Fig. 2B) cell lines. Cells were exposed to an IC_{10} Taxol dose of 3 nM and a range of cisplatin doses, as described in Table I. The effect of Taxol on the cisplatin IC_{50} dose was assessed relative to cisplatin treatment alone (CDDP; sequence A in Table I).

In A2780/CP70 cells (Fig. 2B), the IC_{50} for cisplatin (CDDP) is $150\ \mu M$. When Taxol exposure preceded cisplatin (T>C), the IC_{50} of cisplatin was dramatically reduced to $5\ \mu M$. If cells were exposed to cisplatin first (C>T), or exposed to cisplatin and Taxol together (C+T>T), the cisplatin IC_{50} remained at $150\ \mu M$.

We next examined the time course of the effect of the T>C drug-treatment sequence on cisplatin sensitivity. As shown in Fig. 3A, the IC_{50} of cisplatin (CDDP) for A2780 cells is $18\ \mu M$. When cisplatin exposure was preceded by a 24-hour exposure to $3\ nM$ Taxol (T>C), the IC_{50} was reduced to $12\ \mu M$. When cells were incubated for 24 hours in drug-free media after the Taxol exposure, then treated with cisplatin (T>24>C in Fig. 3A), the cisplatin IC_{50}

was $14\ \mu M$. After a 48-hour (T>48>C) or 72-hour (T>72>C) incubation period between Taxol and cisplatin treatments, the IC_{50} was $40\ \mu M$.

In A2780/CP70 cells (Fig. 3B), the IC_{50} of cisplatin (CDDP) is reached at $150\ \mu M$. When cells were first treated with Taxol for 24 hours, followed immediately by cisplatin (T>C in Fig. 3B), the IC_{50} dose was reduced to $5\ \mu M$. When cells were incubated for 24 hours in drug-free media after the Taxol exposure, then treated with cisplatin (T>24>C), the IC_{50} dose was reduced further to $2\ \mu M$. After a 48-hour incubation interval between Taxol and cisplatin exposures (T>48>C), the IC_{50} was at $8\ \mu M$. There was no Taxol effect on the cisplatin IC_{50} after a 72-hour interval (T>72>C). Thus, Taxol was associated with a dramatic increase in sensitivity to cisplatin in A2780/CP70 cells. Taxol was comparatively ineffective in influencing cisplatin cytotoxicity in A2780 cells.

These data indicate that cisplatin sensitivity in A2780 cells is relatively unaffected by Taxol at this dose. However, in A2780/CP70 cells, the effect of Taxol on cisplatin sensitivity is maximal at 24 hours following Taxol treatment and suggests that at 48 hours after treatment, the effect has begun to revert towards baseline. Thus, Taxol and cisplatin act in a supra-additive fashion in cisplatin-resistant human ovarian cancer A2780/CP70 cells, and this effect is maximal when there is a 24-hour interval between Taxol treatment and cisplatin treatment. Such an effect was not seen in cisplatin-sensitive A2780 cells.

Measurement of Rates of Cellular Cisplatin Accumulation

To determine whether Taxol influences cisplatin drug uptake, we measured the rate of total cellular cisplatin accumulation in A2780 and A2780/CP70 cells during 1-hour cisplatin exposures. The cisplatin doses of $18\ \mu M$ and $200\ \mu M$, respectively, followed a 24-hour treatment with Taxol. Cellular platinum concentration was expressed as nanograms of platinum per million cells. Each data point represents the mean of four determinations. Fig. 4A shows the data for A2780 cells; Fig. 4B shows the data for A2780/CP70 cells. In neither cell line did either Taxol or DMSO affect the cisplatin accumulation profile. Thus, in neither cell line was Taxol associated with increased cellular uptake of cisplatin, and the rate of drug uptake was similar to that seen with DMSO and media controls.

DISCUSSION

At Taxol doses in the nanomolar range, Taxol induces a modest 1.5-fold increase in cisplatin sensitivity in cisplatin-sensitive A2780 cells. In contrast, Taxol causes an increased sensitivity to cisplatin in cisplatin-resistant A2780/CP70 cells so that the IC_{50} decreases from $150\ \mu M$ to less than $5\ \mu M$. This is similar to data regarding Taxol-induced sensitivity to x-irradiation by a log factor of 1.8, or approximately 80-fold (10). In our studies, the Taxol dose was $3\ nM$; in the x-irradiation studies, the Taxol dose was $10\ nM$. It is unclear whether these effects have a

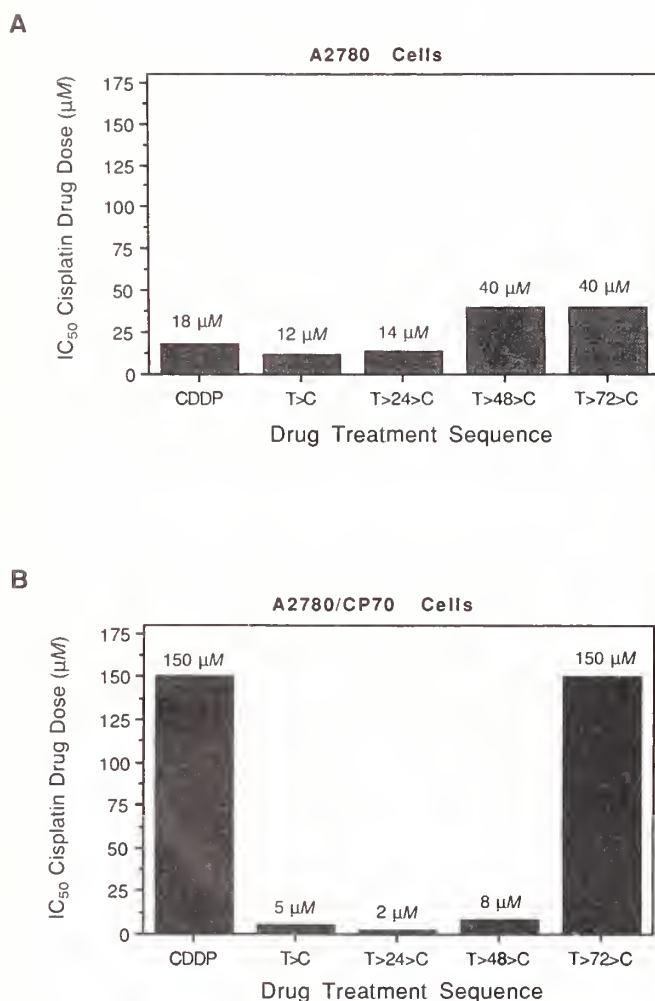
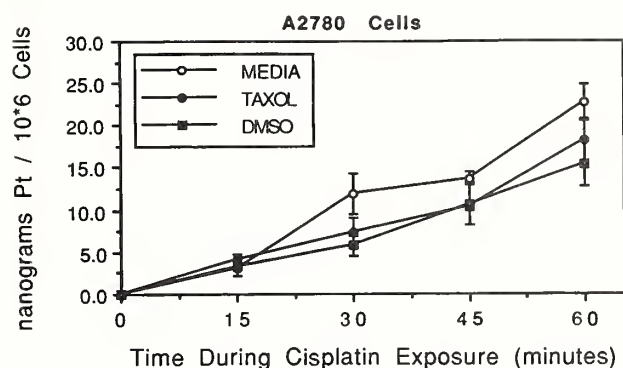


Fig. 3. The time course of the Taxol:cisplatin drug-sequence effect on cisplatin cytotoxicity in A2780 (Fig. 3A) and A2780/CP70 (Fig. 3B) cell lines. Cells were exposed to an IC_{10} Taxol drug dose of $3\ nM$ for 24 hours, after which cells were treated for 1 hour with a range of cisplatin doses, immediately after Taxol (T>C), 24 hours after (T>24>C), 48 hours after (T>48>C), or 72 hours after (T>72>C) Taxol treatment. The effect of Taxol on the cisplatin IC_{50} dose was assessed in comparison with cisplatin treatment alone (CDDP).

A



B

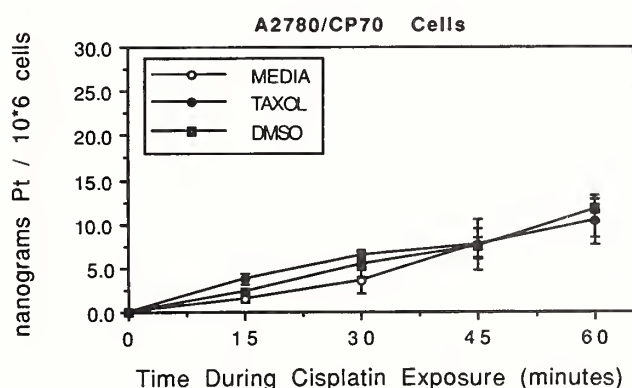


Fig. 4. Cellular accumulation of cisplatin in A2780 (Fig. 4A) and A2780/CP70 (Fig. 4B) cell lines following a 24-hour treatment with an IC_{10} Taxol dose or with DMSO. Each data point is the mean and standard deviation of four separate determinations.

common molecular mechanism, or whether these are indeed separate subcellular effects of a novel anticancer agent.

Taxol is known to induce a block in the progression of cells through the G_2 -M phase of the cell cycle (11). This is thought to at least partially explain the increased sensitivity to x-irradiation. However, cisplatin has been traditionally thought to be relatively cell-cycle nonspecific (12). It is known that cellular resistance to cisplatin is directly related to the efficiency of DNA repair function (7) and that DNA repair efficiency may be related in part to the cell cycle (13). It is therefore possible that the Taxol-related enhancement in cellular sensitivity to cisplatin and to x-irradiation may have a common molecular basis.

However, the mechanisms by which DNA damage is repaired may be different for x-irradiation versus bifunctional DNA damaging agents such as cisplatin. For chemically induced bulky DNA adducts, the nucleotide excision repair (NER) function appears to be the primary mechanism for repair (14). In this system, the initial step appears to be recognition and excision of the DNA damage by a

group of excision repair genes that include ERCC1 and XPA (14). ERCC1 and XPA proteins may not be directly involved in repair of x-irradiation-induced DNA damage. In other studies, we have shown that the changes reported here in cell survival are associated with concurrent down-regulation of DNA repair function, but without changes in mRNA expression levels of ERCC1 or XPA (R.J. Parker and E. Reed, unpublished observations, 1992). Thus, the commonality between the Taxol influence on these two modalities may or may not carry down to the molecular level.

Neither Taxol nor the diluent DMSO had any substantial effect on cellular cisplatin accumulation in these cells. Further, DMSO had no effect on cell kill at the DMSO doses used. It is unclear whether Cremophor EL®, the diluent used for Taxol in clinical preparations, has any effect on A2780/CP70 cells regarding cell kill or cisplatin drug accumulation. However, these studies suggest that the Taxol-cisplatin effect is directly related to Taxol and is independent of the drug diluent. Cremophor EL is thought possibly to relieve some of the Taxol-related allergic side effects but is not necessary for the Taxol-related effects on enhancement of cisplatin cytotoxicity.

The primary clinical implication of our data includes the possibility that when Taxol is administered with DNA-damaging bifunctional chemotherapeutic agents, Taxol should always be administered first. This interpretation is consistent with the original observation in L1210 cells made by Citardi et al. (1). It is of course still unclear whether these observations represent a universal relationship that is true for all malignant cells or whether these data represent only one of several possible outcomes that may occur within a large group of various malignancies.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Taxol and Radiation

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The cytotoxic effects of Taxol and/or ionizing radiation were evaluated in four human tumor cell lines. The recognized antimicrotubular effects of the drug leading to transitory accumulations of cells in the G2/M phase of the cell cycle, the most radiosensitive phase of the cycle, prompted this assessment of the potential for Taxol to function as a cell-cycle, phase-specific radiosensitizer. Taxol alone was cytotoxic to all four cell lines at low (< 25 nM) concentrations. A Taxol concentration of 10 nM for 24 hours led to 48, 15, 8, and 4.4% of cells retaining clonogenic potential for melanoma, two cervical carcinomas, and astrocytoma, respectively. There were significant Taxol concentration-time-dependent differences in response between the cell lines. Cell lines also showed significant differences in their responses to ionizing radiation. Combined treatment resulted in a demonstration of radiation sensitization with the astrocytoma and melanoma cell lines but not with the cervical carcinoma cell lines. Sensitizer enhancement ratios at the 10% cell survival level were 1.8 for 10 nM Taxol for 24 hours with the astrocytoma cells and 1.2 for 40 nM Taxol for 24 hours with the melanoma cells. The cervical carcinoma cell lines showed an additive effect for radiation and Taxol at all drug concentrations; that is, combined treatments elicit an additive or supra-additive response with, however, no simple relationship between Taxol concentration, Taxol time of treatment, and radiation dose in optimizing cytotoxic effectiveness. Combined modality treatments using relatively low concentrations of Taxol and ionizing radiation can result in an enhanced response and, at the least, an additive response, which could be advantageous in a clinical setting. [Monogr Natl Cancer Inst 15:89-94, 1993]

Ionizing radiation treatments represent one of the principal approaches to the control of human cancers, particularly solid tumors. Such treatments provide the advantage of largely confining the therapeutic radiation dose to the tumor volume and, in contrast to many chemotherapeutic agents, the ability to initiate lethal damage in cells in any stage of the cell cycle. However, substantial differences, which are cell-type dependent in part, in sensitivity between cells in different stages of the cell cycle are a common feature of response to conventional photon or electron treatments (1-3). The delivery of radiation dose to the tumor volume as fractions over a period of weeks ameliorates this effect in part since resistant cells (principally those in late S and late G1 phases) will survive and cycle into more sensitive phases of the cycle (principally

G2/M) with time (3). Enhancing the ability of ionizing radiations to cause lethal damage to nominally resistant cells can also be achieved using chemical sensitizers of radiation action. This approach has followed a number of avenues. Agents that are biochemically activated under hypoxia and thereby enhance cellular damage in normally radioresistant G1 hypoxic cells (primarily nitroimidazoles) have provided one approach to combined modality treatments (3). Other approaches have examined the use of growth factors in regulating the cell cycle, or of modifying DNA and enhancing its sensitivity by interfering with purine-pyrimidine metabolism, with DNA-associated enzymes (e.g., topoisomerase inhibitors), or of replacing thymidine with the sensitizing halogenated pyrimidines (S-phase dependent) (4). Agents resulting in the accumulation of cells in late G2 phase and not allowing or slowing the continued cycling and progression of cells through mitosis will lead to the selective accumulation of cells in the most radiosensitive phase of the cell cycle. This cell-cycle phase sensitivity can be seen under some circumstances using radiation alone. Exposure of cells to ionizing radiations leads to induced delays in cellular progression through the cell cycle with this delaying effect being most pronounced for cells in late G2 phase (3). As the radiation dose is delivered at lower dose rates, biological effectiveness usually declines; however, an "inverse dose rate effect" for cell killing has been shown in some instances. That is, there is an optimal dose rate where cells are delayed, accumulated, and rendered susceptible to lethally induced damage. This effect of selective accumulation and killing of cells in the sensitive G2 phase of the cell cycle has been found with one of the cell lines used in this study (5) but not with others (6).

The natural plant product and exploratory chemotherapeutic agent Taxol¹ would appear to have a clear potential for accumulation of cells in the most radiosensitive phase of the cell cycle. The basis of the drug action is to stabilize microtubule structures, thus preventing the microtubular dynamics of a normal mitosis and leading to transitory cell accumulations (7-9).

The recognized properties of this drug and the known variation in radiosensitivity through the cell cycle led to the development of experiments to evaluate the potential for cell-cycle-dependent enhancement of radiation action. The cytotoxic abilities of Taxol at relatively low concentrations have been demonstrated both *in vitro* and *in vivo*, and ongoing clinical trials are evaluating the therapeutic potential of Taxol for a number of normally refractory human tumors (10-12). Ideally, in initiating combined modality protocols involving chemotherapeutic agents and

*See "Notes" section following "References."

ionizing radiations, the effectiveness of the two agents should at least be additive and preferably superadditive with combinations of relatively low doses resulting in a sensitizing response. Initial experiments carried out with a relatively radioresistant human astrocytoma cell line indicated that Taxol led to the accumulation of cells with a G2/M DNA content and that it demonstrated a sensitizing action when Taxol treatment was followed by Cs-137 gamma rays (13,14).

In this study, we report on the effects of gamma rays, of Taxol in a time-dose-dependent manner, and of both agents combined on a number of human tumor cell lines with the overall result that there were significant differences in responsiveness between human tumor cells of different origins.

MATERIALS AND METHODS

The human tumor cell lines used in these studies were derived from human melanoma (SK-MEL-28ATCC no. HTB-72); cervical carcinoma (SiHa; ATCC no. HTB-35 and C-33A; HTB-31); and astrocytoma (Kernohan grade III established in culture from a surgical specimen from the Neurological Institute of New York, Columbia-Presbyterian Medical Center). Cell lines were grown in modified Eagle's medium with Hanks' balanced salts (GIBCO) and 10% fetal calf serum (Hyclone) supplemented with SerExtend, L-glutamine, essential and nonessential amino acids, vitamins, and gentamicin. Cells were subcultured in flasks, maintained at 37.5 °C with 5% CO₂. Cells were routinely monitored for cytology with both general and chromosome-specific counts and rearrangements being assessed. All cell lines were hypotetraploid with different and nonconstant variations in specific chromosomes between cells. Taxol (NSC 125973) was obtained from the National Cancer Institute drug program. A stock solution of 10 mM was prepared in dimethyl sulfoxide and kept at -40 °C until thawed for experimental usage. Ionizing radiation (Cs-137 gamma rays) was delivered at a dose rate of 1.1 Gy/min from an Atomic Energy of Canada Model GC40 irradiator.

Depending on the nature of the observations to be undertaken, cells were cultured in slide flasks, 60-mm dishes, or 100-mm dishes. Asynchronously growing populations were plated out and, after 24 hours attachment and growth, different concentration-time combinations of Taxol were used, followed by irradiation as appropriate. Mitotic cell accumulations and cellular morphology were evaluated microscopically, with the fraction of cells cycling being monitored by bromodeoxyuridine (BrdUrd) uptake (5 μ M) into DNA, fixation *in situ*, and fluorescence examination of a fluorescein-tagged monoclonal antibody against BrdUrd-substituted DNA. Mitotic indices were determined by counting 1000 cell samples and determining the proportion of rounded, chromatin-condensed mitotic cells in relation to all cells. Flow cytometry was undertaken on propidium iodide-stained cells and DNA profiles generated. Clonogenicity studies were undertaken

in 100-mm dishes with cells being replated at appropriate cell numbers to generate 70 to 100 clones per dish. Colony formation in complete medium or complete medium plus Taxol for a continuous exposure took place over 14 to 20 days, following which the medium was discarded and fixative (cold methanol, 3 parts: acetic acid, 1 part) gently added. After at least 1 hour fixation, fixative was discarded, dishes were rinsed, and Giemsa stain was added. Macroscopically visible colonies of greater than 50 cells were counted and related to the number of cells plated. Results are expressed relative to controls.

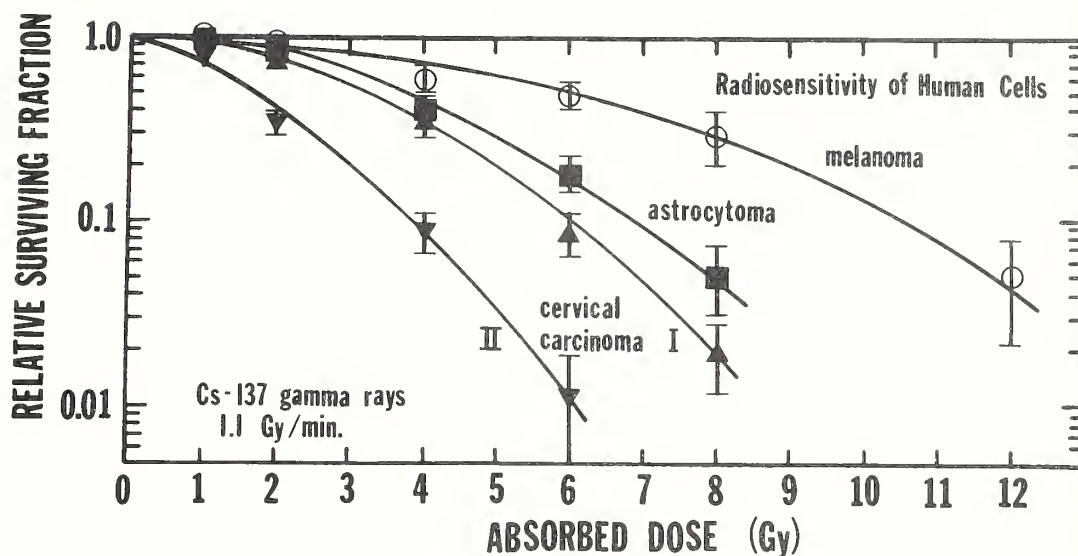
RESULTS AND DISCUSSION

Mitotic Cell Accumulations and Cellular Morphology Following Taxol

For all four human tumor cell lines examined, Taxol resulted in a time- and concentration-dependent increase in the fraction of mitotic cells. Peak mitotic indices tended to be at 8 to 12 hours with declines thereafter. By 48 hours posttreatment, mitotic indices were in all instances the same as or lower than control frequencies with a significant fraction of cells showing multiple micronuclei. This had been noted previously with the astrocytoma cells (13). That is, cells initially accumulated in mitosis, then attempted division with a nonfunctioning spindle, resulting in aberrant postmitotic cells with a G2 rather than a G1 DNA content (14). In general, the frequencies of control cells with a G2 DNA content were 15 to 20%, but this can increase to 90 to 100% after Taxol treatment (13). This indicates that the majority of treated cells have cycled to mitosis but then failed to complete a normal DNA halving and remained with a G2 DNA content. Overall, all four human tumor lines were sensitive to Taxol concentrations at less than 100 nM and usually at less than 10 nM. The accumulation of mitotic cells and the morphological appearance of cells were consistent with Taxol deleteriously influencing normal mitotic spindle function.

Radiation Sensitivity of Human Tumor Cells

Asynchronous cells from each tumor cell line were exposed to a graded series of doses from 1 to 12 Gy of Cs-137 gamma rays, and clonogenicity results are shown in Fig. 1. Results indicate that the melanoma cells are the most radioresistant with one of the cervical carcinoma lines the most sensitive. These findings are consistent with earlier results (5,6) and also with the clinical responsiveness of the particular tumors. That is, there are large differences in radiosensitivity between tumor cells of different origins and in large part *in vitro* responsiveness correlates with clinical observations. At the 50% survival level, there is a factor of 4 difference in dose between the sensitive cervical carcinoma cells and the most resistant melanoma cells, with the astrocytoma cells and the other cervical carcinoma cells being different by factors of 2.5 and 2.2, respectively. All results are expressed relative to control, with mean plating efficiencies being 17, 58, 44,



and 26% for the melanoma, astrocytoma, and the least and most sensitive cervical carcinoma cells, respectively.

Taxol Sensitivity of Human Tumor Cells

Taxol concentrations ranging from 0.1 to 100 nM were used during the course of these experiments for cell contact times ranging from 2 hours to continuous. Continuous contact means Taxol was added to cells and was not removed for the entire period of cell incubation and colony formation. Fig. 2 shows the combined results from the four tumor lines for 24-hour drug contact on asynchronous cells. It is clear that there are substantial differences between human cells of different origins in their sensitivity to Taxol, and these differences are not the same as those seen with ionizing radiation. The nature of the dose response curves also appears to vary between the different cell lines. In all four instances, there is a relatively steep initial response followed by a lessened response at higher dose levels. This differential sensitivity between cells within a tumor cell line and between tumor cell lines could be interpreted as indicating that some fraction of cells (differing between cell lines) requires greater concentrations of drug to destroy their clonogenic capacity. Although there may be partially resistant subpopulations of cells within each tumor cell line, there are even larger differences between the cell lines. At a concentration of 10 nM for 24 hours, the percentages of cells relative to control expressing clonogenic potential were 48, 15, 8, and 4.4 for the melanoma, cervical carcinoma I and II, and astrocytoma cell lines, respectively. The basis for this drug-concentration-time-dependent effect between the different cell lines is not known. Clearly, however, this spindle interacting agent is efficient at relatively low (<25 nM) concentrations. In no instance did treatment of cells with 0.1 nM Taxol result in a difference from control; however, 1 nM Taxol for 24 hours (or more) resulted in small divergences from control levels. Fig. 3

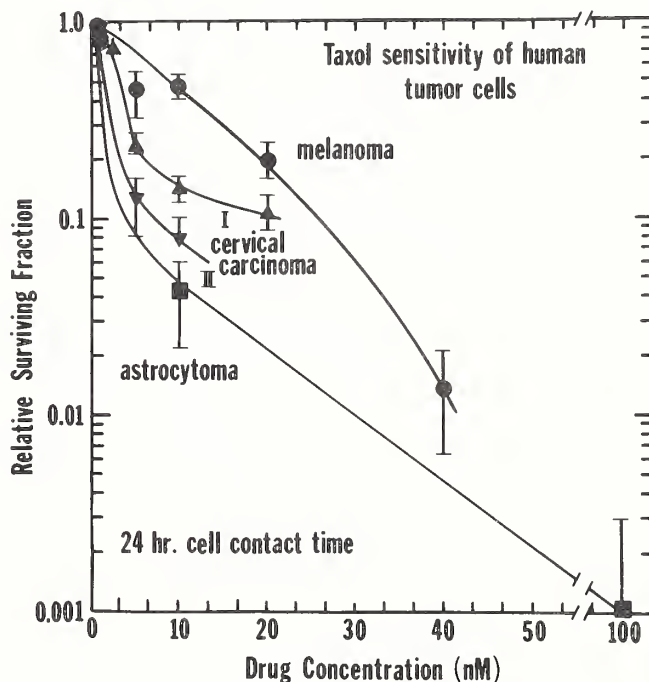


Fig. 2. Taxol responsiveness of human tumor cells. Relative surviving fraction is plotted against Taxol concentration in nM. Taxol was added to asynchronous cell populations for 24 hours. Error bars represent SEM and lines are meant to guide the eye.

shows results obtained for the cervical carcinoma I line and the astrocytoma cell line when cells were exposed to 10 nM Taxol for different periods of time. Even a 2-hour exposure of the astrocytoma cells resulted in some cell death. Continuous exposure of the cervical carcinoma cells resulted in a relative surviving fraction of 9.5×10^{-3} (~1%), whereas a similar treatment of the astrocytoma

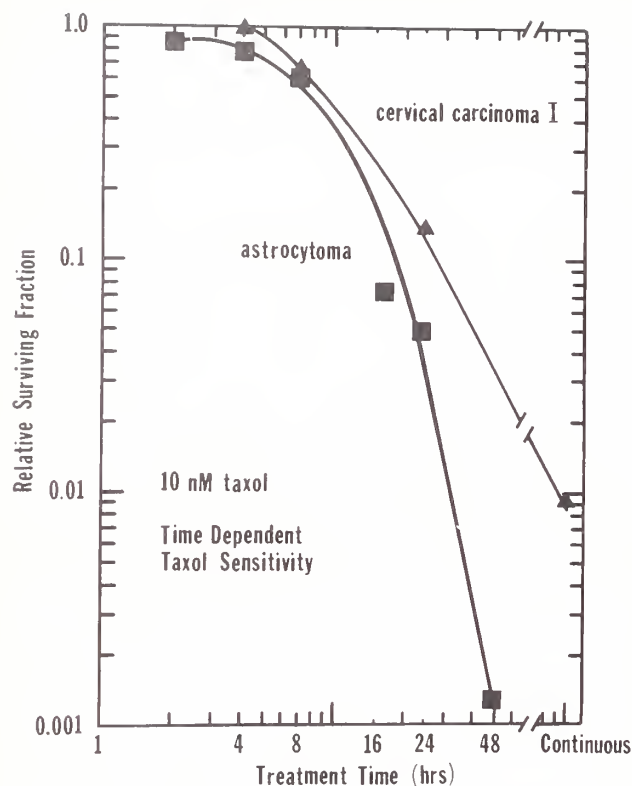


Fig. 3. Taxol time-dependent responsiveness of human tumor cells. Relative surviving fraction is plotted against Taxol treatment time in hours for 10 nM Taxol. Results are shown for one of the cervical carcinoma cell lines and the grade III astrocytoma cell line.

cells resulted in a relative surviving fraction of 3.8×10^{-5} ($\sim 0.004\%$). These results show that there are large concentration-time-dependent differences in the cell killing ability of Taxol between the different tumor cell lines, but, nevertheless, in all cases cells are sensitive at relatively low Taxol levels.

Effects of Taxol and Radiation

Initially, asynchronous populations of cells were treated with different concentrations of Taxol for 24 hours, then irradiated with graded doses of gamma rays. Clonogenicity was assessed, and results expressed relative to Taxol treatments are shown in Figs. 4 and 5. If the cytotoxic effects of Taxol at any concentration and of radiation are independent and additive, then survival curves will essentially be superimposable. If, however, the Taxol pretreatment results in enhanced radiation induced lethality divergence from the radiation-alone curve results. Such is seen in Fig. 4 for the melanoma and astrocytoma cell lines. At 10% cell survival, the sensitizer enhancement ratio (the ratio of doses to produce the same biological effect) is 1.8 for 10 nM Taxol on astrocytoma cells [as shown previously, (14)] and 1.2 for 40 nM Taxol on melanoma cells. For the melanoma cells, results obtained with 1, 2, 5, and 10 nM Taxol were not different from radiation alone. The 1 and 2 nM results are not shown. Clearly, the radiosensitization found with the astrocytoma cells is not seen at all with the same Taxol concentration (10 nM) on the melanoma cells; however, there is some radiosensitization at 40 nM. It should be noted that at

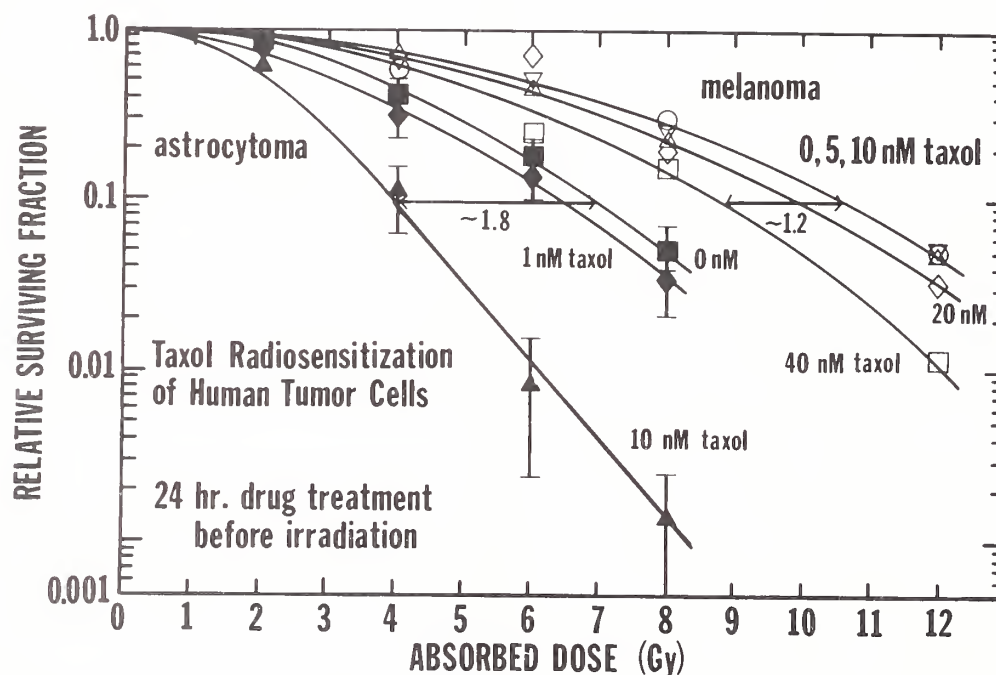


Fig. 4. Radiation-Taxol responsiveness of human tumor cells. Relative surviving fraction is plotted against absorbed dose of Cs-137 gamma rays (at a dose rate of 1.1 Gy/min). Taxol at different concentrations was added to asynchronous cells 24 hours before irradiation. Results are expressed relative to Taxol alone, with lines meant to guide the eye. Sensitizer enhancement ratios at 10% survival are shown for 10 nM Taxol on the astrocytoma cells and 40 nM Taxol on the melanoma cells.

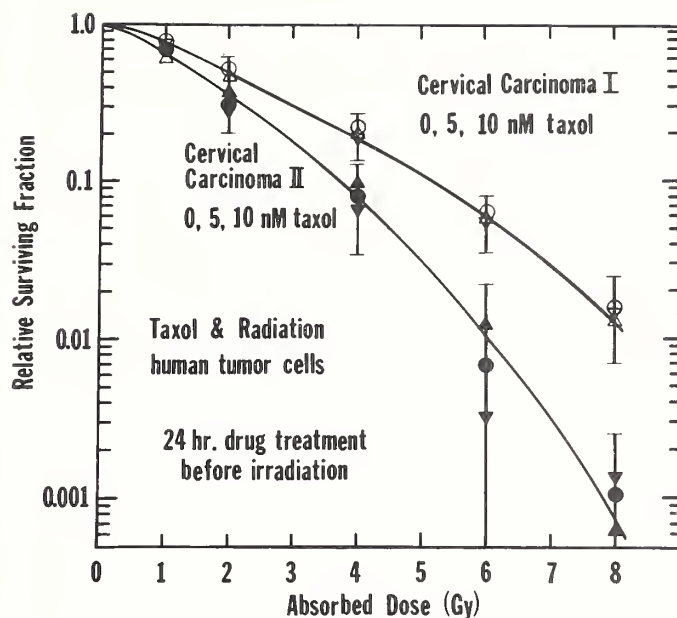


Fig. 5. Radiation-Taxol responsiveness of human tumor cells. Relative surviving fraction is plotted against absorbed dose for two human cervical carcinoma cell lines. Taxol at different concentrations was added to asynchronous cells 24 hours before irradiation. Lines are meant to guide the eye, with data presented relative to Taxol alone. There is no Taxol enhancement of radiation response.

these Taxol levels only a small fraction of cells survive a 24-hour treatment, 4.2 and 1.5% for the astrocytoma and melanoma cells, respectively. When results of Taxol pretreatment at any concentration, including 0.1 and 1 nM, which are not shown, are compared with radiation alone on the cervical carcinoma cell lines (Fig. 4), there are no differences from a strictly additive effect. It is possible that differences could arise at higher, more cytotoxic Taxol concentrations, as was seen with the Taxol and radiation-resistant melanoma cells; however, over the dose range used, which is similar to that for the responsive astrocytoma cells, there is no indication of radiosensitization of the cervical carcinoma cells. Also, if Taxol is effecting a cellular delay in a relatively small fraction of cells (<10%) in other more radioresistant stages of the cell cycle, this might be difficult to detect but would strongly influence the radiation dose response curve. Overall, the effects of Taxol and radiation on these human tumor cells of different origins are at least additive and in two instances supra-additive. There is, then, no simple relationship between Taxol concentration, Taxol time of treatment, and radiation dose in optimizing cytotoxic effectiveness, and the ideal time for irradiation relative to mitotic cell accumulations may readily differ between cell lines. Additionally, cells from the various cell lines may remain held at the G2/M boundary for different times before attempting a mitosis that would frequently result in a postmitotic cell with a G2 DNA content. Nevertheless, the promise remains that combined modality treatments

using relatively low concentrations of Taxol and ionizing radiation could result in an enhanced response, but at least combined treatments elicit an additive response, which could be advantageous in a clinical setting.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Taxol and Lipopolysaccharide Activation of a Murine Macrophage Cell Line and Induction of Similar Tyrosine Phosphoproteins

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Taxol, a unique antimitotic drug, is thought to exert its antitumor activity by binding to and promoting the assembly of microtubules. Studies on the mechanism of action of Taxol have focused mainly on this ability to induce microtubule polymerization. Recent evidence suggests that Taxol affects novel intracellular targets within macrophages and neutrophils. To investigate further the mechanism of action of Taxol on macrophages, we have examined the pattern of tyrosine protein phosphorylation, using antiphosphotyrosine monoclonal antibodies (MAbs) in a RAW 264.7 (RAW) macrophage cell line. We found that Taxol, like lipopolysaccharides (LPS), caused a marked increase in tyrosine phosphorylation of three proteins having M_r of 40 (p40), 41 (p41), and 43 (p43) kd in RAW cells. Immunoprecipitation of these tyrosine phosphoproteins followed by Western blotting with a microtubule-associated protein-2 (MAP-2) kinase MAb revealed that both Taxol and LPS induced the tyrosine phosphorylation of a MAP-2 kinase-like protein. In addition, MAP-2 kinase-like activity was stimulated in the presence of Taxol or LPS. Examination of cellular mRNA levels in LPS and Taxol-activated macrophages by Northern blot analysis revealed increased expression of Interleukin-1 β , and tumor necrosis factor- α cytokine mRNAs. Because Taxol promotes tubulin assembly, we examined the effect of LPS on microtubule polymerization. LPS had no polymerizing activity over Taxol alone. We conclude that Taxol and LPS have a common target in macrophages that is a critical component of the signal transduction pathway that mediates LPS cellular responses. [Monogr Natl Cancer Inst 15:95-101, 1993]

Taxol,¹ a unique antitumor agent isolated from the plant *Taxus brevifolia*, is thought to exert its activity by binding to and promoting the assembly of microtubules both in vivo and in vitro (1,2). This action of Taxol renders microtubules resistant to depolymerization and essentially nonfunctional, thereby blocking cells in late G₂ and M phases of the cell cycle (3). It is becoming increasingly clear that alternate mechanisms of action exist that may account for Taxol's activity as an anticancer agent. One such mechanism involves the interaction of Taxol with the protooncogene *c-mos*, pp^{39mos}, or its growth regulatory pathway. This protein kinase was found to phosphorylate tubulin in vitro and to colocalize with tubulin and microtubules both in vivo and in vitro (4,5). These data

suggest that both pp^{39mos} and Taxol may act via a common intracellular pathway resulting in modification of the microtubule network and in formation of the spindle apparatus.

Another mechanism of Taxol is suggested by the recent finding that Taxol, like lipopolysaccharides (LPS) can activate macrophages to secrete the cytokine, tumor necrosis factor- α (TNF- α) (6,7). More specifically, the addition of Taxol or LPS to murine macrophages resulted in increased release of TNF- α and in down-regulation of TNF- α receptors. This effect was shown to be specific for the LPS-inducible system in macrophages, as the induction of interferon- γ receptors, an LPS-insensitive pathway, was unaffected by either agent. Furthermore, TNF- α release and receptor expression in LPS-hyporesponsive C3H/HeJ mice was unaffected by treatment with Taxol. These data suggest that LPS and Taxol may exert their effect through a common signal transduction pathway in macrophages.

In an effort to elucidate the mechanism(s) by which LPS activates macrophages, Weinstein et al. (8) investigated whether tyrosine phosphorylation of specific intracellular proteins played a role in LPS-induced macrophage activation. Their results showed that the addition of LPS to murine macrophages induced tyrosine phosphorylation of several cytoplasmic proteins of M_r p41, p42, p43.5, p44 kd as well as higher molecular weight species. To determine whether Taxol might function in a similar manner, we have prepared cell lysates from Taxol or LPS-treated RAW cells and examined the induction of tyrosine phosphoproteins by Western blot analysis using an antiphosphotyrosine monoclonal antibody (MAb). The results indicate that Taxol and LPS share a common signal transduction pathway and suggest that Taxol has, in addition to a direct antitumor effect on target cells, an alternate mechanism of action that may be mediated through macrophage activation.

MATERIALS AND METHODS

Chemicals

Taxol was obtained from Hauser Chemical Company (Boulder, Colo.), dissolved in dimethylsulfoxide (DMSO) at 10 mg/mL, and stored at -20 °C. Control cells received comparable volumes of DMSO not to exceed 0.1%. LPS, myelin basic protein, aprotinin, phenylmethylsulfonyl fluoride (PMSF), okadaic acid, protein kinase inhib-

*See "Notes" section following "References."

itor, and adenosine triphosphate (ATP) were obtained from Sigma Chemical Company (St. Louis, Mo.). Leupeptin was obtained from Boehringer Mannheim (Indianapolis, Ind.). γ -[32 P]-ATP was purchased from DuPont NEN Research Products (Boston, Mass.).

Cell Culture and Stimulation

RAW 264.7 cells (1.5×10^6 cells/well) were cultured for 16 hours in six-well plates containing 1.5 mL Dulbecco's modified Eagle's medium (GIBCO, Inc., Grand Island, N.Y.) supplemented with 10% fetal calf serum (GIBCO) after which the stimulant was added for the times indicated. Taxol was tested for contamination of bacterial endotoxin by a Quantitative Chronogenic Limulus Amebocyte Lysate Test (Whittaker Bioproducts, Baltimore, Md.) as per the manufacturer's instructions and found to be less than 1 pg/mL, the detectable limit of the Limulus test.

Preparation of Cell Lysates

After stimulation of RAW macrophages with LPS or Taxol, the cells were washed twice with ice cold phosphate-buffered saline (PBS) containing 1 mM sodium orthovanadate and lysed in 200 μ L of cold lysis buffer (20 mM Tris-Cl, pH 8.0, 137 mM NaCl, 10% glycerol [wt/vol], 1% Triton X-100 [wt/vol], 1 mM sodium vanadate, 2 mM ethylene glycol-bis-(beta-aminoethyl ether) *N,N'*-tetraacetic acid [EGTA], 1 mM PMSF, 20 mM leupeptin, 0.15 U aprotinin) for 20 minutes at 4 °C. Detergent insoluble material was pelleted by centrifugation ($10\,000 \times g$ for 5 minutes) at 4 °C.

Assay of Myelin Basic Protein Kinase Activity

Incubations were performed in triplicate at 30 °C according to the method of Gomez et al. (9) with modifications. Briefly, 50 μ L reactions contained 25 mM Tris-Cl, pH 7.0, 0.1 mM EGTA, 0.1 mM sodium orthovanadate, 1 μ M okadaic acid, 1 μ M protein kinase inhibitor, myelin basic protein (0.33 mg/mL), RAW cell extract, 10 mM magnesium acetate, 100 μ M cold ATP, and 0.1 mM γ -[32 P]-ATP (2×10^6 cpm/nmol). After 20 minutes at 30 °C, the reaction was stopped by the addition of 10% sodium dodecyl sulfate (SDS). The phosphorylated products were resolved by separation on 15% SDS-polyacrylamide gels and autoradiographed using Kodak X-Omat AR-5 film and a DuPont Lightning Plus intensifying screen for 5 hours at -70 °C.

Western Blot Analysis

A protein determination of the supernatant fractions was done by bicinchoninic acid (BCA) assay (Pierce Chemicals, Rockford, Ill.), and approximately 100 μ g of protein was added to each well of a 12% SDS-polyacrylamide gel electrophoresis (PAGE) followed by electrophoretic transfer (Hoeffer Scientific Instruments, San Francisco, Calif.) for 5 hours at 0.5A onto

polyvinylidene difluoride (PVDF)-immobilon membranes. The filters were blocked in 3% bovine serum albumin 0.15 M NaCl, and 50 mM Tris, pH 7.4, and subsequently incubated with MABs to either phosphotyrosine (Upstate Biotechnology, Inc., Lake Placid, N.Y.) (1:1000) or MAP-2 kinase (Zymed Laboratories, South San Francisco, Calif.) (1:2000) for 3 hours. After washing, filters were incubated with goat-antimouse alkaline phosphatase (GAM-AP) (Promega, Inc., Madison, Wis.), diluted 1:7500 for 1 hour, washed and developed with 5-bromo-4-chloro-3-indolyl phosphate/nitroblue tetrazolium (BCIP/NBT) (Promega, Inc.) as substrates.

RNA Preparation

RAW cells (1×10^8) were stimulated with LPS (1 μ g/mL), Taxol (10 μ M), or media containing 0.1% DMSO. Cells were harvested after 4 hours and total cellular RNA was prepared by guanidinium thiocyanate methodology and purified by centrifugation through cesium chloride. RNA samples (30 μ g) were fractionated by electrophoresis in 1.2% agarose/formaldehyde gels before transfer onto GeneScreen Plus nylon membranes (Dupont NEN Research Products, Boston, Mass.). DNA probes for murine β -actin, TNF- α , and IL-1 β were made using specific 5' and 3' oligonucleotides (Clontech Laboratories, Palo Alto, Calif.) to do reverse transcription-polymerase chain reaction (PCR) from RAW 264.7 cell mRNA. After PCR, these probes were purified using agarose gel electrophoresis. Nick-translated DNA probes (4×10^6 cpm/mL) for TNF- α and IL-1 β were hybridized with the nylon membranes at 42 °C in 6 \times saline-sodium phosphate-EDTA (SSPE), 1 \times Denhardt's solution, 50% formamide, 0.5% SDS, 10% dextran sulfate, and 100 μ g/mL salmon sperm DNA. The membranes were washed with several changes of 2 \times standard saline solution (SSC) containing 0.5% SDS at room temperature and several changes of 0.2 \times SSC containing 0.5% SDS at 60 °C.

In Vitro Polymerization of Microtubules

Calf brain tubulin was prepared by two cycles of assembly-disassembly according to Shelanski et al. (10). Tubulin monomer (10 μ M), LPS (1 μ g/mL), or a combination of Taxol plus LPS was incubated at 37 °C in morpholino-ethane-sulfonic acid (MES) buffer (0.1 M MES, 1 mM EGTA, 0.5 mM MgCl_2 , pH 6.6). The assembly of microtubules was measured by recording a change in optical density at 350 nm ($\text{OD}_{350 \text{ nm}}$) every minute over a 40-minute period, using a DU-70 Beckman spectrophotometer (Beckman Instruments, Fullerton, Calif.). This is one representative experiment out of six.

Immunoprecipitation

RAW cells (5.0×10^6) were stimulated with Taxol (10 μ M) or LPS (1 μ g/mL) for 30 minutes and solubilized in lysis buffer as described above. Protein concentration was determined by BCA assay and adjusted to 1 mg/mL. The immunoprecipitation reaction mixture contained 1 mL of

lysate to which 40 μ L of a 50% suspension of antiphosphotyrosine-agarose beads (1 mg/mL) (Upstate Biotechnology, Inc.) was added. This mixture was incubated at 4 °C on an end-over-end rotator for 4 hours. The beads were centrifuged at $500 \times g$ for 5 minutes and washed three times with lysate buffer at 4 °C. The phosphotyrosine-containing proteins were eluted with PBS containing 5 mM phenylphosphate for 30 minutes at room temperature, electrophoresed on a 12% SDS-PAGE, transferred to PVDF membranes, and probed with anti-MAP-2 kinase MAb.

RESULTS

Induction of Tyrosine Phosphorylation After Taxol Stimulation

Western blot analysis using an antiphosphotyrosine MAb revealed that the addition of Taxol to RAW 264.7

murine macrophage cells caused the induction of tyrosine phosphorylation of three proteins ($M_r = 40, 41,$ and 43 kd), which mimicked the LPS effect (Fig. 1). These proteins are collectively referred to as p40-43. Addition of either Taxol or LPS for 60 minutes caused a diminution in tyrosine phosphorylation of p40, whereas phosphorylation of the p41 and p43 substrates was increased in Taxol-treated cells. In LPS-stimulated cells, all three proteins decreased by 60 minutes. Several other phosphotyrosine-containing proteins were also detected (p25, p65, p80); however, these did not undergo any significant modulation upon Taxol or LPS stimulation. In these experiments the concentration of Taxol was optimized to 10 μ M (unpublished observation), which is the same concentration of Taxol used for induction of microtubule assembly. Stimulation of murine macrophages with phorbol myristic acetate caused the induction of tyrosine phosphoproteins different from those induced by LPS or Taxol. There was a modest induction of p40 and p41, whereas there was a

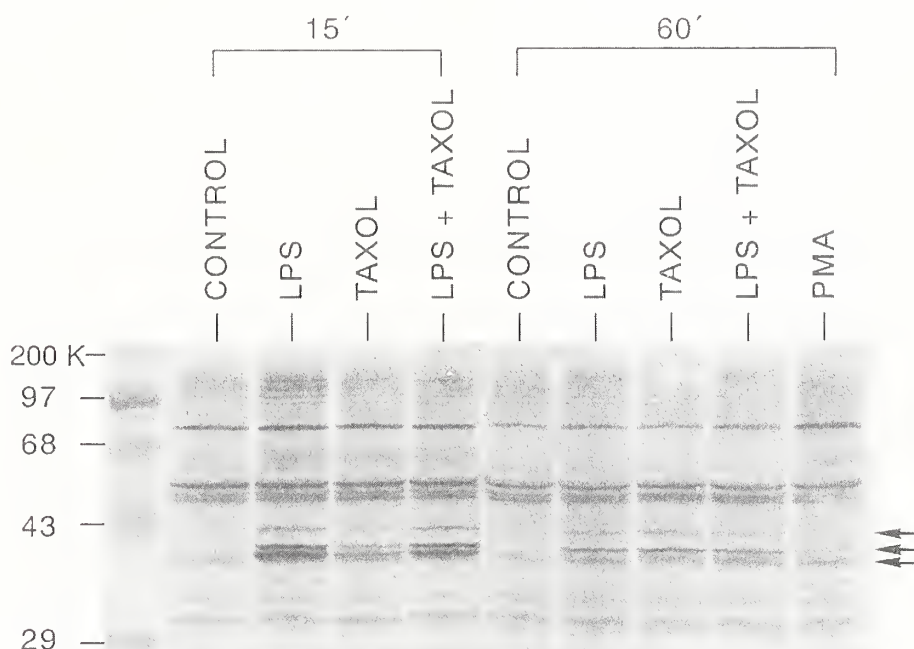


Fig. 1. Induction of tyrosine phosphorylation in RAW 264.7 cells as shown by Western blot analysis using an antiphosphotyrosine MAb. Cells were incubated with LPS (1 μ g/mL), Taxol (10 μ M), or PMA (100 nM) for the times indicated. Cellular lysates, containing equal amounts of protein, were run on 12% SDS-PAGE gels, transferred to PVDF membranes, and reacted with a MAb to phosphotyrosine as described in "Materials and Methods." The addition of Taxol and/or LPS caused the induction of three tyrosine phosphoproteins (arrows) having apparent molecular masses of 40, 41, and 43 kd.

complete absence of tyrosine phosphorylation of the p43 protein. These results are in agreement with those of Weinstein et al. (8), substantiating their observation that LPS-induced tyrosine phosphorylation involves a protein kinase C-independent mechanism.

Activation of this signal transduction pathway by other antitumor compounds such as colchicine, vinblastine, vincristine, doxorubicin, and mitomycin C ($10 \mu\text{M}$ each) showed that only Taxol was able to induce phosphorylation of these proteins, suggesting that this effect is specific for Taxol and not for other mitotic spindle poisons or antitumor compounds (data not shown).

It was shown previously that stimulation of RAW murine macrophages (6) and peritoneal macrophages (6,7) with Taxol caused the release of $\text{TNF-}\alpha$ from these cells (6). To ensure that the induction of tyrosine phosphorylation of p40-43 occurred in response to Taxol and not in response to Taxol-induced $\text{TNF-}\alpha$ secretion, we examined the direct effect of $\text{TNF-}\alpha$ on macrophage activation. $\text{TNF-}\alpha$ had no effect on induction of tyrosine phosphoproteins (data not shown). We also activated cells with LPS or Taxol in the presence of a neutralizing antibody to $\text{TNF-}\alpha$, which resulted in no changes in the level of tyrosine phosphorylation observed (data not shown). These data show that Taxol and LPS induce an indistinguishable pattern of macrophage protein tyrosine phosphorylation and support the idea that both agents activate a common signal transduction pathway.

Tyrosine Phosphorylation of MAP-2 Kinase in RAW Macrophages After Stimulation with Taxol and LPS

We next attempted to identify the tyrosine phosphoproteins by Western blot analysis using a MAb that was raised against a synthetic peptide corresponding to a 21 amino acid sequence of MAP-2 kinase (17). MAP-2 kinase proteins were chosen as a potential target because activation of a variety of cells by mitogens has been shown to induce the tyrosine phosphorylation of a family of proteins having M_r of ~ 40 kd. These kinases have been identified as members of the extracellular-signal-regulated kinases (12). When immunoblots of total cellular extracts from unstimulated, LPS-, or Taxol-stimulated RAW cells were probed with antiMAP-2 kinase antibody, a protein (or proteins) that comigrated with p40-43 was detected. Taxol- and LPS-activated cells as well as unstimulated cells contained similar levels of p40-43 MAP-2 kinase-like proteins (Fig. 2A). Since MAP-2 kinases require both tyrosine and serine/threonine phosphorylation for activation of their kinase activity (13), we examined the cellular lysates for tyrosine phosphorylation of MAP-2 kinase-like proteins. In this experiment, cellular lysates were first immunoprecipitated with phosphotyrosine antibodies and then blotted with an antiMAP-2 kinase MAb. Antiphosphotyrosine MAbs immunoprecipitated MAP-2 kinase-like proteins only in those cells that were stimulated by either Taxol or LPS (Fig. 2B). These results indicate that

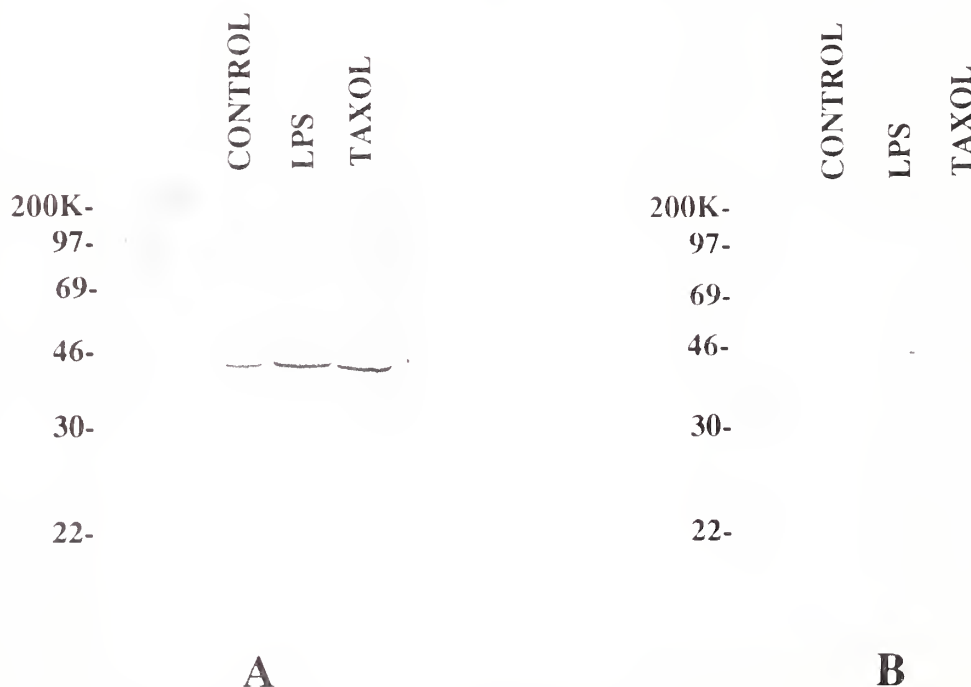


Fig. 2. Identification of MAP-2 kinase in lysates of Taxol or LPS-treated RAW cells. A) RAW cells were stimulated with Taxol ($10 \mu\text{M}$) or LPS ($1 \mu\text{g/mL}$) for 30 minutes. Cells were lysed and fractionated on 12% SDS-PAGE gels and probed with antibodies to MAP-2 kinase. B) RAW cells were stimulated as in Fig. 2A but were solubilized in Triton X-100 lysis buffer containing protease and phosphatase inhibitors, immunoprecipitated with antiphosphotyrosine antibodies linked to agarose, released with 5 mM phenylphosphate, and the supernatant processed as in Fig. 2A for cell lysates. The immunoblots were probed with a MAb to MAP-2 kinase. The results show that MAP-2 kinase proteins are phosphorylated only in response to Taxol and/or LPS.

the tyrosine phosphorylation of MAP-2 kinase-like proteins is modulated by both Taxol and LPS.

Activation of MAP-2 Kinase in RAW Cells After the Addition of Taxol and LPS

We next determined whether the Taxol or LPS-induced phosphorylation of a MAP-2 kinase-like protein results in increased MAP-2 kinase-like activity in RAW cells. Cellular extracts of Taxol and LPS-stimulated cells were assayed for MAP-2 kinase-like activity using myelin basic protein as substrate (14). MAP-2 kinase-like activity was induced by both Taxol and LPS (Fig. 3). The time course of activation of MAP-2 kinase-like protein by LPS was maximal at 15 minutes, and stimulation by Taxol was maximal at 30 minutes (Fig. 3). These results show that MAP-2 kinase-like phosphorylation induced by the addition of Taxol or LPS resulted in activation of endogenous MAP-2 kinase-like activity.



Fig. 3. Time course of MAP-2 kinase activation by Taxol and LPS. RAW macrophages were treated with Taxol (10 μ M) or LPS (1 μ g/mL) for the indicated times. Cellular lysates were prepared as described in "Materials and Methods," and aliquots were assayed for MAP-2 kinase activity using myelin basic protein as substrate in the presence of γ -[32 P]-ATP. MAP-2 kinase-like activity was induced by both Taxol and LPS.

Effect of Microtubule Polymerization After Stimulation by LPS and Taxol

To further clarify the roles played by Taxol and LPS upon signaling pathways in macrophages, we determined whether LPS could modulate the assembly of microtubules in a fashion similar to Taxol. It has recently been shown that LPS binds to tubulin using a method that utilized 125 I-labeled LPS crosslinked by treatment with a photoreactive agent, sulfosuccinimidyl 2-(p-azidosalicylamido) ethyl-1,3'-dithiopropionate and by coelution through a gel filtration column (15). Using an in vitro tubulin polymerization assay with twice-cycled microtubule protein ($2 \times$ MTP), we show that LPS alone (0 to 100 μ g/mL) was unable to induce tubulin assembly, whereas a characteristic hyperbolic polymerization curve was achieved in the presence of Taxol (3) (Fig. 4). Therefore, LPS must have different targets within the microtubule network that do not involve tubulin assembly.

Induction of Cytokine Expression After Stimulation by LPS and Taxol

To further determine that Taxol and LPS activate macrophages via a common signal transduction pathway, we investigated whether Taxol could augment the expression of two important macrophage-derived cytokines, TNF- α and IL-1 β , both of which are stimulated by LPS (16). Northern blot analysis of LPS or Taxol-treated cells indicated that TNF- α and IL-1 β mRNA levels were induced significantly after 4 hours of treatment, whereas the level of β -actin mRNA remained unchanged (Fig. 5). Using reverse transcription/PCR methodology, we also observed an increase in IL-6 mRNA in both Taxol and LPS-treated cells after 24 hours of treatment (data not shown). The physiological significance of cytokine production on the antitumor effect of Taxol has yet to be addressed.

DISCUSSION

The antitumor activity of Taxol has been attributed primarily to its ability to promote and stabilize microtubule polymerization and thus arrest cells in G₂ and M phases of the cell cycle. In this study, we examine the effects of Taxol directly on a macrophage cell line, RAW 264.7. Our results show that Taxol acts via an intracellular pathway that is similar to the LPS activation pathway in macrophages. This mechanism involves tyrosine phosphorylation of several proteins having M_r of ~ 40 kd, one of which is a MAP-2 kinase-like protein. Stimulation of this intracellular signal transduction pathway by either Taxol or LPS also results in the activation of macrophages in MAP-2 kinase-like activity and induction of the cytokines, IL-1 β , and TNF- α .

The role of the microtubule network in macrophage activation is not unique to Taxol. Recent studies have examined the responses of other microtubule poisons on the activation of macrophages (17). In the myelomono-

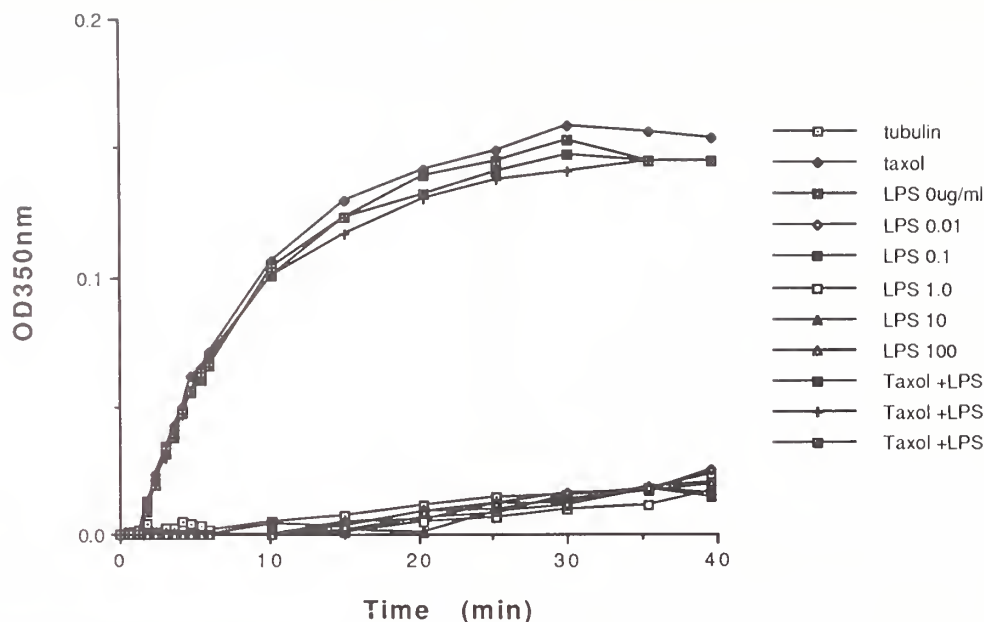


Fig. 4. Effect of Taxol and LPS on microtubule assembly. Calf brain tubulin was prepared by two cycles of assembly-disassembly ($2 \times$ MTP). $2 \times$ MTP ($10 \mu M$) was incubated with $10 \mu M$ Taxol, $10 \mu M$ Taxol plus $1 \mu g/mL$ LPS in triplicate (1-3) or 0.01, 0.1, 1.0, 10, or $100 \mu g/mL$ LPS. The assembly of microtubules was measured at $37^\circ C$ by a change in OD 350 nm. Taxol, but not LPS, induced the assembly of microtubules. The combination of LPS and Taxol did not result in any significant increase in microtubule assembly over Taxol alone. This is one representative experiment of six.

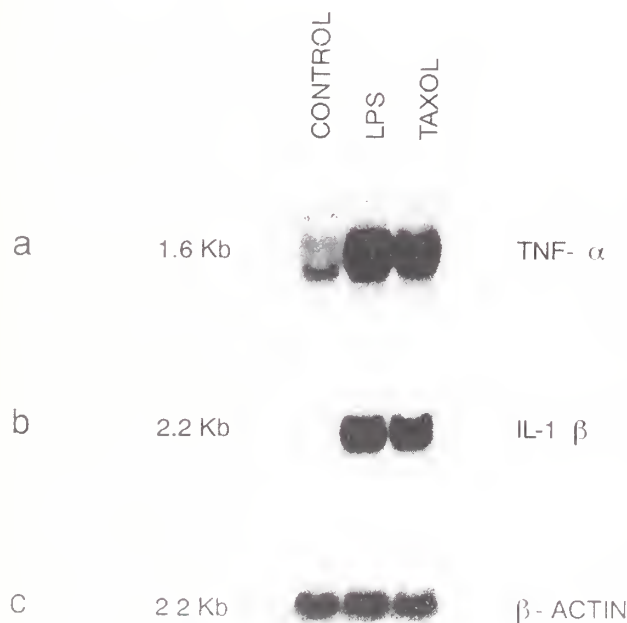


Fig. 5. Northern blot analysis of RNA from RAW cells stimulated with Taxol or LPS. Total cellular RNA was extracted from RAW macrophage cells that were unstimulated (control), stimulated with LPS ($1 \mu g/mL$), or stimulated with Taxol ($10 \mu M$) for 4 hours at $37^\circ C$. Equal amounts of total RNA ($30 \mu g/well$) were fractionated on 1.2% agarose/formaldehyde gels, transferred to GeneScreen Plus nylon filters, and hybridized with 4×10^6 cpm/mL DNA probes for (a) TNF- α , (b) IL-1 β , and (c) β -actin mRNA. mRNA for TNF- α and IL-1 β are induced to similar levels by both Taxol and LPS.

cytic THP-1 cell line and in adherent peripheral blood mononuclear cells, the production of IL-1 β was found to be potentiated 15- to 30-fold by agents that disassemble microtubules, i.e., colchicine, vinblastine, and vincristine. However, cytochalasin B, an inhibitor of actin filament assembly, had no effect on IL-1 β production (17). Therefore, the induction of the macrophage cytokine, IL-1 β , by these agents suggests that the microtubule, but not the actin cytoskeletal network, mediates the IL-1 β response. This paper shows that Taxol also activates macrophages, possibly through the microtubule network.

In our studies, Taxol and LPS induced in macrophages the tyrosine phosphorylation of three proteins (p40-43), one of which is a MAP-2 kinase-like molecule. MAP-2 kinases are thought to be important in the phosphorylation cascade of mitogen-activated signal transduction pathways and in cell cycle control regulation (18). Upon activation, MAP-2 kinase is believed to phosphorylate MAP-2 (19) and protein S6 kinase (20), both of which are important in cell cycle regulation. We have shown that Taxol and LPS stimulate a signal transduction pathway in macrophages that results in activation of MAP-2 kinase-like protein(s). Presumably, this MAP-2 kinase-like member becomes activated upon the addition of Taxol or LPS and subsequently phosphorylates a substrate associated with the microtubule network, which leads to macrophage activation. Alternatively, Taxol may interact with a component of the microtubule network, which results in MAP-2-like kinase activation leading to signals necessary for macrophage activation. In either case, LPS and Taxol appear to have common intracellular targets.

Examination of Taxol for contamination with LPS showed that Taxol was not contaminated with endotoxin.

A comparison of the chemical structure of LPS with that of Taxol does not reveal any structural similarity that may account for the common intracellular targets between these two molecules. Thus, activation of macrophages by Taxol appears to result from an overlap in the cellular machinery involved in LPS signal transduction and Taxol's activity. This argument is strengthened by recent reports that have shown that LPS, in addition to binding to cell surface receptors, has an intracellular target that may include β -tubulin and MAP-2 (15). These data, along with the findings reported here, suggest that the microtubule network may be an intracellular target for both Taxol and LPS in macrophages.

NOTE ADDED IN PROOF

Since the submission of this manuscript, a paper appeared describing similar observations on the effects of LPS and Taxol on tyrosine phosphorylation in murine macrophages (21).

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Part of this work was presented at the 21st Annual Meeting of The American Society for Cell Biology (22).

Intraperitoneal Administration of Taxol in the Management of Ovarian Cancer

Maurie Markman, Eric Rowinsky, Thomas Hakes, Bonnie Reichman, Walter Jones, John L. Lewis, Jr., Stephen Rubin, John Curtin, Richard Barakat, Lois Almadrones, William Hoskins*

The safety and pharmacology of the intraperitoneal administration of Taxol was evaluated by treatment of 25 patients (24 with ovarian cancer) on a phase I dose-escalation trial. The drug was delivered in 2 L of normal saline every 3 to 4 weeks, with a starting dose of 25 mg/m². The dose-limiting toxicity was abdominal pain at Taxol doses greater than 125 mg/m². A 3-log pharmacokinetic advantage for peritoneal cavity exposure to Taxol, compared to the systemic compartment, was demonstrated following intraperitoneal delivery. In addition, high levels of Taxol persisted within the cavity for more than 48 hours following a single treatment. Despite the major pharmacokinetic advantage for peritoneal cavity exposure, significant concentrations of Taxol were demonstrated within the systemic compartment after intraperitoneal treatment. Several patients exhibited clinical and laboratory evidence of an antitumor response. Further exploration of a possible role for the intraperitoneal administration of Taxol in the management of ovarian cancer appears indicated. [Monogr Natl Cancer Inst 15:103-106, 1993]

INTRAPERITONEAL THERAPY IN THE MANAGEMENT OF OVARIAN CANCER

Over the past decade, investigators at several institutions have explored the potential use of the intraperitoneal administration of cytotoxic and biological agents as therapy for patients with ovarian cancer (1). The major goal of this therapeutic strategy is to expose tumors within the peritoneal cavity to higher concentrations of antineoplastic agents for longer periods of time than can be achieved safely with systemic drug administration.

For agents whose cytotoxicity against ovarian cancer has been demonstrated in either clinical or experimental systems to be concentration-dependent (2-4), or where resistance may be overcome by increasing the concentration of the drug in contact with the tumor (5,6), there is a strong rationale to consider intraperitoneal drug delivery for therapy of this tumor, as it remains principally confined to the peritoneal cavity in the majority of patients for most of its natural history (7-9). Objective antitumor responses, including surgically documented complete responses, have been observed with many cytotoxic and

biological agents delivered directly into the peritoneal cavity as therapy of ovarian cancer in the salvage (second-line) setting (1).

WHY CONSIDER TAXOL FOR INTRAPERITONEAL ADMINISTRATION IN OVARIAN CANCER?

Taxol¹ is a cytotoxic antineoplastic agent that results in tumor cell kill by causing excessive polymerization of tubulin and dysfunctional microtubules (10). For the following reasons, this unique cytotoxic drug is particularly attractive as a candidate for intraperitoneal delivery in the treatment of ovarian cancer (also see Table 1):

1) Several phase II trials have demonstrated that the agent has major activity when administered systemically to individuals with ovarian cancer, most notably patients with clinically defined platinum-resistant disease (11-13).

2) Recent evaluation has shown that Taxol undergoes metabolism in the liver (14,15). This feature is known to significantly increase the pharmacokinetic advantage associated with peritoneal cavity exposure compared to that of the systemic compartment, following regional drug administration (1,16-18).

3) Examination of several cell lines has demonstrated that the biological effects of Taxol appear to be dependent both on the duration of exposure and on the drug concentration in contact with the tumor, two features that may be optimized with intraperitoneal delivery (19). For example, when LC8A lymphoblasts were exposed to Taxol for 2 hours, the percentage of cells with microtubular bundles increased from 15 to 65% as the Taxol concentration was increased from 0.1 μ M to 10 μ M. Conversely, at a fixed Taxol concentration of 1 μ M, the percentage of cells with bundles increased from 25 to 75% as the duration of exposure was increased from 2 to 22 hours (19). While these data are limited, they do support the potential importance of both dose-response and duration of exposure in optimizing the cytotoxicity of Taxol.

4) Finally, it should be noted that Taxol is not considered to be a vesicant, an important feature for an agent considered for direct peritoneal cavity instillation (1).

PHASE I TRIAL OF INTRAPERITONEAL TAXOL

On the basis of these preclinical and clinical data, investigators at the Memorial Sloan-Kettering Cancer Center,

*See "Notes" section following "References."

- Table 1.**—Rationale for considering the intraperitoneal administration of Taxol in the management of ovarian cancer
1. Demonstrated activity of Taxol in patients with platinum-refractory ovarian cancer
 2. Demonstrated hepatic metabolism of Taxol, potentially significantly increasing the pharmacokinetic advantage associated with intraperitoneal delivery
 3. Demonstration in several nonovarian cancer cell lines that the activity of Taxol is dependent on both the concentration of the drug in contact with the tumor and the duration of exposure, features that can be optimized with intraperitoneal delivery
 4. Lack of vesicant properties of Taxol

with the assistance of the Pharmacology Laboratory of the Johns Hopkins Oncology Center, conducted a Gynecologic Oncology Group-sponsored phase I trial of Taxol administered by the intraperitoneal route (20) (Table 2). The treatment plan called for patients to receive the Taxol dose delivered in 2 L of normal saline every 3 to 4 weeks.

The starting dose of Taxol was 25 mg/m². The dose was to be escalated if unacceptable toxicity was not encountered, but inpatient dose escalation was not permitted. All patients received a standard pretreatment program (dexamethasone, benadryl, ranitidine) to prevent Taxol-associated hypersensitivity reactions (21). In most patients, treatments were administered in the outpatient setting.

Twenty-five patients entered this phase I trial, of whom 24 had ovarian cancer. In general, the treatment was reasonably well tolerated until the 175 mg/m² Taxol dose level was reached. At this level, two of five patients experienced severe abdominal pain with therapy (narcotic analgesia required and pain significantly interfered with the patients' normal daily activities). At the 200 mg/m² dose level, three of four patients developed severe abdominal pain. At the 125 mg/m² dose level, none of four patients complained of severe pain, although one patient did experience moderate pain (narcotic analgesia required, but pain did not interfere with normal daily activities). In all patients the pain subsequently resolved and there were no apparent long-term consequences associated with intraperitoneal Taxol delivery (e.g., late episodes of bowel obstruction).

Table 2.—Summary of results of the phase I trial of intraperitoneal Taxol

1. Dose-limiting toxicity: abdominal pain at single intraperitoneal Taxol doses >125 mg/m²
2. Bone marrow suppression observed at intraperitoneal Taxol doses ≥175 mg/m²
3. Objective evidence of antineoplastic activity (falls in CA-125 levels, decreases in malignant ascites) observed
4. Peritoneal cavity exposure to Taxol (as measured by AUC) following intraperitoneal administration exceeded that of the systemic compartment by a ratio of 1000:1
5. Despite the major pharmacokinetic advantage demonstrated for cavity exposure following intraperitoneal Taxol delivery, the drug was measured in the systemic compartment at concentrations previously demonstrated to cause significant biological effects

Bone marrow suppression, particularly neutropenia, is a major side effect of Taxol administered systemically (10–13). In this intraperitoneal trial, significant marrow suppression was not observed until the 175 mg/m² dose level. At this level, all five treated patients were found to have a white blood cell count below 2000/mm³, although only a single patient developed a white count below 1000/mm³.

Although this was a phase I trial and demonstration of efficacy was not a major study end point, several objective responses in patients with platinum-refractory ovarian cancer were observed. These responses included significant decreases in the level of serum CA-125 determinations, compared to baseline values (six patients), and disappearance of malignant ascites (two patients).

Perhaps the most interesting and important observation of this trial was the pharmacokinetics associated with the intraperitoneal administration of Taxol. Peak peritoneal cavity levels ranged from 19 to 324 μM/L. Approximately 22% of the administered intraperitoneal dose was cleared from the cavity during the first 24 hours after delivery. Details of this analysis have been published previously (20).

However, measurable levels of Taxol were detected in the systemic compartment following intraperitoneal delivery. The peak plasma levels were observed within 1 hour after regional delivery and ranged from unmeasurable levels to 0.86 μM/L. The measurable levels of Taxol attained in the plasma following intraperitoneal administration have been associated with major biological effects (10).

The ratio of the area-under-concentration (AUC) versus time curve for the peritoneal cavity following intraperitoneal delivery of Taxol, compared to that of the systemic compartment, was approximately 1000:1. From a pharmacologic standpoint, this observed advantage for peritoneal cavity exposure following intraperitoneal delivery makes Taxol equivalent to the best agents examined for regional administration (1). However, of equal importance, significant systemic levels of Taxol were attained following intraperitoneal instillation, suggesting delivery to tumor by both direct diffusion and capillary flow when the cytotoxic agent is administered by the intraperitoneal route.

FURTHER EXPLORATION OF A ROLE FOR INTRAPERITONEAL TAXOL IN THE MANAGEMENT OF OVARIAN CANCER

Unfortunately, in this initial phase I trial of intraperitoneal Taxol administered every 3 to 4 weeks, the dose-limiting toxicity was abdominal pain. On the basis of the significant pharmacokinetic advantage associated with the intraperitoneal delivery of the agent, it might be possible to deliver a lower dose of the drug on a more frequent dosing schedule, but with less local toxicity.

Such a modified regimen is currently under investigation in a Gynecologic Oncology Group-sponsored trial at the Memorial Sloan-Kettering Cancer Center. It is anti-

pated that the Gynecologic Oncology Group will further evaluate the activity of intraperitoneal Taxol in the phase II setting when the current phase I trial is complete.

POTENTIAL ROLE FOR INTRAPERITONEAL TAXOL IN THE MANAGEMENT OF OVARIAN CANCER

Assuming that activity for intraperitoneal Taxol can be documented in patients with small volume residual ovarian cancer, particularly in the setting of documented platinum resistance, where might this treatment strategy be considered in the standard management of individuals with ovarian cancer (Table 3)?

If it can be shown that the intraperitoneal delivery of Taxol results in significant levels of drug reaching the systemic compartment, it would be reasonable to consider this route of drug delivery for patients with small volume disease as part of their initial chemotherapy program along with an organoplatinum drug administered intraperitoneally or systemically. If inadequate concentrations of Taxol are shown to reach the systemic compartment following regional delivery at the maximally tolerated dose, it would be reasonable to consider the administration of intraperitoneal and intravenous Taxol in the management of a similar patient population.

In patients with small volume residual disease following initial systemic chemotherapy, intraperitoneal Taxol (with or without an organoplatinum drug) may be considered a reasonable salvage program. However, in the relatively near future it is quite possible that most patients with ovarian cancer will be receiving Taxol as part of their initial chemotherapy program, and the activity of intraperitoneal Taxol (or any other treatment regimen) in this setting will need to be carefully defined.

Intraperitoneal Taxol might also be considered as part of a consolidation program after a high-dose organoplatinum/alkylating agent chemotherapy program. The extremely high local concentrations of Taxol achieved in the peritoneal cavity following intraperitoneal delivery might be effective in killing small volume microscopic residual disease remaining after a high-dose regimen.

Table 3.—Potential roles for intraperitoneal Taxol in the management of ovarian cancer

1. As part of an initial chemotherapy program for patients with small volume residual disease (following initial surgical tumor debulking) along with an organoplatinum drug, with the Taxol delivered only by the intraperitoneal route or both regionally and systemically
2. As a salvage chemotherapy program for patients with small volume residual disease, either alone or with another cytotoxic agent (i.e., cisplatin)
3. As part of a consolidation program after high-dose intravenous chemotherapy or in patients with high-grade tumors who achieve a surgically documented complete response following a systemically administered treatment program

Similarly, intraperitoneal Taxol could be considered as a consolidation program for patients with high-grade tumors who achieve a surgically documented complete response to non-Taxol-containing systemic regimens, as it is now known that the ultimate relapse rate in this patient population approaches 50 to 60% (22,23). In this setting, Taxol could be administered alone or combined with another agent, such as cisplatin, carboplatin, or recombinant interferon.

Ultimately, a role for the intraperitoneal administration of Taxol, or any other agent in the management of ovarian cancer, will need to be demonstrated in a phase III randomized clinical trial. However, considerable work remains to be done to define an optimal intraperitoneal Taxol regimen to test in such a study.

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NOTES

¹Taxol is used in this manuscript to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Neurotoxicity of Taxol

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Neurotoxicity, manifested primarily by a motor and sensory polyneuropathy, is the principal nonhematological side effect of Taxol. Available evidence suggests that Taxol produces a toxic effect involving either axons or ganglion cell bodies, or both, rather than a myelinopathy. As with other toxic polyneuropathies, patients with preexisting peripheral neuropathies, such as those caused by diabetes mellitus or ethanol, appear to be particularly predisposed to developing neurological toxicity. The incidence and severity of the neuropathic manifestations also appear to be related to the Taxol dose level, the cumulative dose of Taxol, and possibly to the use of Taxol in combination with cisplatin. Rarely, manifestations of autonomic and central nervous system dysfunction occur. Taxol also induces myalgias in the peri-treatment period, especially when used in high doses, and a myopathy has been noted in patients treated with high doses of Taxol administered alone and in combination with cisplatin. Although dose-response relationships for Taxol have not been clearly established, these neuromuscular effects are likely to become a significant clinical problem if higher doses of Taxol are used with hematopoietic colony-stimulating factors. The neuromuscular effects of Taxol, including symptoms, physical and electrophysiological manifestations, and predisposing factors, as well as agents that may be used for neuroprotection, are discussed in this report. [Monogr Natl Cancer Inst 15:107-115, 1993]

Although hematopoietic growth factors appear to ameliorate the neutropenia associated with Taxol,¹ which is the agent's principal toxicity, neuromuscular toxicity limits treatment with high single and cumulative doses of Taxol used alone or in combination with other antineoplastic agents (1,2). Neuromuscular toxicity is particularly prominent when Taxol is administered at high doses to heavily pretreated patients and in combination with cisplatin, a regimen that is likely to be used in treating patients with ovarian, lung, and, possibly, head and neck cancers.

PRECLINICAL STUDIES

While the neurotoxicity associated with Taxol has been well defined, little is known about its pathogenesis. In fact, although neurites are rich in microtubules and other classes of microtubule-disrupting agents, such as the vinca alkaloids, frequently induce peripheral neurotoxicity, little

is known about the function of microtubules in neural processes and in the pathogenesis of neurotoxicity. Early studies have implicated microtubules in the outgrowth and stabilization of neurites, as well as in the normal suppression of filopodial activity along neurites proximal to the growth cone (3-6). Ultrastructural studies have shown that microtubules and neurofilaments in the neurite terminate in the growth cone, which is vital to cell movement and dendrite growth (6-8). Microtubules have been described as the "railroad tracks" for fast axonal transport, and membrane vesicles traveling along them are evidently delivered to the sites where the microtubules end (9). Several studies have indicated that microtubules determine where growth cones can occur, and they may do so by controlling the delivery of membrane components (10). Microtubules also provide structural support for neurons, interact with other vital cytoskeletal proteins such as neurofilaments, interact with adhesion molecules, and may be involved in the transport of other essential materials (11-13). In addition, nerve growth factor may become associated with cytoskeletal elements (14,15) and nerve growth factor binding sites have been demonstrated on both microtubules and neurofilaments (16). Microtubules may also affect the mobility of integral membrane proteins and modulate the distribution of nerve growth factor receptors on neuronal surfaces (17).

Taxol has been demonstrated to inhibit neurite growth, which may be related to the induction of microtubule bundles and arrays in neurites (18,19). Taxol also induces prominent morphologic effects such as microtubule bundles in neurons, satellite cells, and Schwann cells in organotypic dorsal root ganglion-spinal cord cultures (18-25). Although these perturbations appear to be particularly prominent in Schwann cells (18,19,24,25), the pathophysiological consequences of Taxol-induced microtubule arrays in Schwann and satellite cells, and even in neuronal cells, are still unclear. Several studies have suggested that Taxol adversely alters microtubule integrity in neurites, indirectly affecting vital interactions with actin, neurofilaments, and substratum attachment sites (11). In addition, treatment of PC12 pheochromocytoma cells that possess many characteristics of mature sympathetic neurons, with both Taxol and cytochalasin D, an inhibitor of neurofilament formation, dramatically augments nerve growth factor receptor-like immunoreactivity, which exceed levels obtained with each agent alone (17). Taxol has also been shown to inhibit the regenerative response of axons and Schwann cells after nerve-crush injuries (26,27). In contrast, Taxol has not been documented to affect the release of neurotransmitters, such as acetylcholine, in

*See "Notes" section following "References."

synaptosomes or neurite formation in neuro-2a neuroblastoma cells (28,29). On the basis of these experimental data, the importance of microtubules in axonal transport and other vital neuron functions, and the fact that neurotoxicity has been a major toxicity of other antimicrotubule drugs, neurotoxicity might have been expected to be a principal toxicity of Taxol in animal toxicology studies and in clinical trials. However, neurotoxicity was not apparent in studies in mice, rats, and dogs, which may have been because of the limitations of those screening models in detecting this effect (30).

NEUROTOXICITY: SINGLE-AGENT TAXOL STUDIES

Schedule

Neurotoxicity was not observed in early phase I studies of Taxol administered on single-dose, intermittent multiple-dose, and 3-hour infusion schedules (31-33). However, these schedules were abandoned early in phase I development because of a high incidence of severe hypersensitivity reactions that primarily occurred with shorter infusion schedules (34). Because clinical experience with these schedules was limited during early clinical evaluations, with only small numbers of patients receiving multiple courses of treatment, it was not possible to determine the relative incidences in neurotoxicity between brief and protracted infusion schedules. The neurotoxicity that is induced by Taxol has primarily been observed when the agent is administered on longer 6- and 24-hour infusion schedules, the most extensively studied schedules to date. Although peripheral neuropathy is a relatively common adverse effect (1,2,35-45), it is rarely clinically significant at Taxol doses below 170 to 200 mg/m². In a review of 402 patients who participated in phase II and III Taxol trials that used a 24-hour infusion schedule, severe grades 3 to 4 neurotoxicity occurred in 0%, 2%, and 10% of patients at Taxol doses below 150 mg/m² and to 151 to 190 mg/m² and above 190 mg/m² (Bristol-Myers Squibb; data on file). Both the incidence and severity of various neurotoxic manifestations appear to be dose related, but neurotoxicity has rarely been dose limiting when Taxol is administered at clinically relevant single-agent doses that do not require the concurrent use of granulocyte colony-stimulating factor (G-CSF) to ameliorate severe neutropenia. Neutropenia has generally been the dose-limiting toxicity of Taxol at conventional single-agent doses (135 to 250 mg/m²) administered over 6 and 24 hours (35-44). However, both peripheral neurotoxicity and neutropenia precluded the dose escalation of Taxol above 250 mg/m² (6-hour infusion) and 275 mg/m² (24-hour infusion) in two early phase I studies involving patients with advanced solid tumors (36,38). Peripheral neuropathy also precluded the dose escalation of Taxol above 250 mg/m² (24-hour infusion) in combination with G-CSF in ovarian cancer patients who received extensive prior treatment with platinum-based therapies (1); the recommended phase II dose of Taxol was 250 mg/m² +

G-CSF. In contrast, although all patients receiving Taxol doses of 315 to 390 mg/m² (24-hour infusion) in a phase I study in refractory leukemias developed mild-to-moderate neurotoxic symptoms, mucositis was determined to be the principal dose-limiting nonhematologic toxicity in this population (41). However, the majority of the patients did not receive more than two courses because of tumor progression, and, therefore, the cumulative neurological effects of Taxol at these higher doses could not be adequately assessed.

NEUROTOXICITY: TAXOL-BASED COMBINATION CHEMOTHERAPY

Taxol-Cisplatin (Without G-CSF)

Although many Taxol-based combination chemotherapy regimens are currently being evaluated, the Taxol-cisplatin regimen has been the most extensively studied regimen to date (2,45). This is largely because of the activity of both agents in advanced ovarian and non-small-cell lung cancers (44,46-50). In a phase I study of Taxol and cisplatin, minimally pretreated patients received alternating sequences of Taxol (110 to 200 mg/m²) and cisplatin (50 to 75 mg/m²) (45). Neutropenia was the principal dose-limiting effect of the drug combination, precluding dose escalation of Taxol above 135 to 170 mg/m² in combination with cisplatin 75 mg/m². Although neurotoxicity was initially anticipated to be formidable because of the overlapping neurotoxic effects of both agents, peripheral neuropathy was a relatively minor side effect within the limited dose ranges that were evaluated. In fact, only 11 of 41 (27%) patients who were evaluable for neurotoxicity developed either symptomatic or objective evidence of neuropathy as detected by sequential neurologic histories and examinations. At these doses, neurotoxic manifestations were never severe (grade 3), nor did they interfere with neurological function. In addition, neurological symptoms were disproportionately greater than objective findings on physical examination and nerve conduction studies (NCS). Neurotoxicity was mild (grade 1) in all cases with the exception of three patients who developed moderate (grade 2) neuropathic signs and symptoms. These patients were the only three patients in the study who had histories of significant alcohol use and evidence of a preexisting alcohol-induced neuropathy on both pretreatment physical examinations and NCS.

Neurotoxicity appeared to be both cumulative and dose related (45). With the exception of the three patients with pretreatment evidence of alcohol-induced peripheral neurotoxicity, manifestations of neurotoxicity were evident only after multiple courses (more than four) at the four lower dose levels (iterations of Taxol 110 to 135 mg/m² and cisplatin 50 to 75 mg/m²). However, neurotoxic signs and symptoms were more common and more pronounced after fewer numbers of courses (one to two) in patients treated at the two highest dose levels (Taxol 170 to 200 mg/m² and cisplatin 75 mg/m²). In general, these effects were also more pronounced than those observed at

comparable doses of either Taxol or cisplatin in single-agent studies. In circumstances in which there was adequate follow-up time after the discontinuation of therapy, neurotoxic manifestations did not progress and, in fact, resolved within several months.

Although electrophysiologic testing did not reveal any evidence of drug-induced autonomic nervous system dysfunction, several patients also experienced significant orthostatic symptoms, including two patients with near syncopal episodes and signs and symptoms of orthostatic hypotension. Electroencephalograms (EEG) and computerized tomography (CT) of the brain were unremarkable in both patients. These near syncopal events, as well as signs and symptoms of orthostatic hypotension, always occurred in the first week after treatment, quickly resolved, and were usually associated with malaise, nausea, vomiting, and anorexia. Therefore, central volume loss, and not autonomic dysfunction, likely accounted for orthostatic manifestations.

Taxol-Cisplatin (+ G-CSF)

The sequence of Taxol before cisplatin at doses of 135 to 170 mg/m² and 75 mg/m², respectively, was recommended for phase II and phase III trials. Although these doses were similar to those that have been associated with activity in ovarian cancer, the maximum tolerated dose for Taxol when combined with cisplatin was much less than the single dose considered safe for solid tumor patients (200 to 250 mg/m²). Therefore, a trial designed to evaluate the feasibility of using G-CSF to further escalate the dose of Taxol in combination with cisplatin was subsequently performed (2). Neutropenia was not dose limiting at Taxol doses as high as 350 mg/m² combined with cisplatin 75 mg/m² and G-CSF, but peripheral neuropathy, myopathy, and severe myalgias were the principal dose-limiting effects of the drug combination. Table 1 depicts the numbers of patients and courses associated with various dose-limiting hematologic and nonhematologic toxicities at each dose level. Recommended phase II doses were Taxol 250 mg/m² combined with cisplatin 75 mg/m² and G-CSF 5 µg/kg/day because of the high proportion of patients developing dose-limiting effects, principally neuromuscular toxicities, at higher doses. Detailed sequential neurological examinations and electrophysio-

logical studies were performed in 21 of 32 patients. At the doses of Taxol and cisplatin used in the study with G-CSF, 20 of the 21 patients who had complete studies developed a neuropathy and 4 patients had objective evidence of a myopathy (2,51). Although neurotoxicity was cumulative at Taxol doses less than or equal to 250 mg/m² in combination with cisplatin 75 mg/m² and was usually symptomatic at cumulative Taxol doses above 600 mg/m², neurotoxicity that interfered with neurological function (grades 3 to 4) was not experienced by any patients at these doses. Therefore, severe neurotoxicity precludes dose escalation of Taxol above 250 mg/m² with or without cisplatin when G-CSF is used. The extent of abnormalities on NCS, especially decrements in sensory nerve action potential (SNAP) and peroneal motor amplitudes, also correlated with the total cumulative dose of Taxol and roughly correlated with the clinical grade of neurotoxicity and the duration of therapy (51). Decrements in SNAP and peroneal nerve amplitudes also correlated with cumulative dose (51).

In contrast, severe neurotoxicity affecting neurological function occurred in all patients treated with one to two courses of Taxol at doses above 250 mg/m² combined with cisplatin doses of 75 to 100 mg/m². Similar to the previous study involving lower drug doses, the onset of neurotoxic signs and symptoms occurred earlier, and these toxicities were more severe in patients with a preexisting peripheral neuropathy secondary to either ethanol or diabetes mellitus.

Neurotoxicity was especially profound in a 51-year-old previously untreated male with esophageal carcinoma, a history of adult-onset insulin-dependent diabetes mellitus, and a mild peripheral neuropathy detected on physical examination and NCS. Approximately 7 days after receiving his first course of Taxol 350 mg/m² followed by cisplatin 75 mg/m², he developed severe numbness and paresthesias, particularly in his distal lower extremities. He was also unable to ambulate because of both weakness and an inability to perceive the position of his limbs. Physical examination revealed severe sensory dysfunction with profound abnormalities in vibratory discrimination and proprioception up to the level of the hips. There was also evidence of proximal motor weakness, but sensory abnormalities were disproportionate to motor abnormali-

Table 1. Taxol-cisplatin + G-CSF: Neurotoxicity grade versus dose

Dose, mg/m ²		New patients	Median courses/patient	Neurotoxicity grade				
Taxol	Cisplatin			0	1	2	3	4
135	75	3	3	1	1	1		
170	75	3	5	1	1	1		
200	75	3	4	2	1			
250	75	10	4	3	4	3		
300	75	8	4	1	2	1	4	
350	75	3	2			2*		1 [†]
250	100	2	1		2*	1		

*Dose de-escalated in four patients due to severe nonheme toxicities.

[†]Patient taken off study due to severe neurotoxicity.

ties. NCS revealed reductions in bilateral sural, median, and ulnar sensory nerve amplitudes indicative of an axonal neuropathy. However, electrophysiologic examination of the peroneal motor nerve was unchanged compared to baseline. Electromyograph (EMG) studies showed the presence of myopathic motor unit action potentials in peroneal muscles. A biopsy of the rectus femoris muscle was subsequently performed, which revealed changes indicative of a toxic myopathy (see section on myopathy and myopathic effects). Although the patient's neurological deficits progressively improved thereafter, significant residual sensory deficits were evident 1 year after treatment, especially involving proprioception, light touch, and pain sensations.

CLINICAL MANIFESTATIONS

The neurotoxic manifestations of Taxol can be divided into those indicative of 1) a sensory neuropathy; 2) a motor neuropathy; 3) an autonomic neuropathy; 4) a myopathy and/or myopathic effects; and 5) a central nervous system toxicity.

Sensory Neuropathy

Symptoms. A sensory neuropathy is the most commonly reported neurotoxic effect of Taxol. A sensory neuropathy invariably occurs when the dose of Taxol approaches 250 mg/m^2 , whether used alone or in combination with cisplatin, and usually precludes dosing at higher doses. The most common initial symptoms include numbness, tingling, and/or burning pain in a glove-and-stockings distribution. Although the distal lower extremities are usually affected first in most patients, many patients report the simultaneous onset of symptoms in the toes and fingers. Perioral numbness has also been described (36). Typically, the symptoms are symmetrical in a length-dependent fashion, although initial symptoms may also be asymmetrical at the onset progressing in a symmetrical pattern (42).

Symptoms may begin as early as 24 to 72 hours after treatment with high single doses ($\geq 250 \text{ mg/m}^2$) (36,40,41), but the neurotoxicity is typically cumulative, with symptoms progressing after each treatment at both high and low doses. The sensory symptoms are generally tolerable, but may be disabling, especially in patients treated at Taxol doses greater than or equal to 250 mg/m^2 alone (36,38) or in combination with cisplatin (2,51) and at lower doses in patients who may be at high risk for developing Taxol-induced neurotoxicity (see "Risk Factors" section).

Neurological examination. The neurological examination characteristically reveals sensory loss to vibration in a distal symmetrical glove-and-stockings pattern. Proprioceptive abilities are also affected if the neuropathy is severe. The latter impairs function and is more likely to occur with high single doses. In fact, loss of large fiber (vibration and proprioception) sensation occurs more frequently than loss of small fiber (pain, temperature) sensation.

Deep tendon reflexes are also frequently reduced or absent, again with distal (ankle) reflexes being affected early. Simultaneous loss of all reflexes can occur with high dose regimens.

Nerve conduction studies. NCS also confirm the sensory loss seen clinically with SNAP amplitudes reduced in a distal length-dependent fashion. Sural SNAP amplitude is virtually always reduced in symptomatic patients. Lipton et al. reported absent sural sensory response in three of four patients who had NCS (42). In one patient with an absent sural sensory response, the ulnar sensory response was absent and the median SNAP amplitude was reduced. Sarosy et al. reported the results of NCS in two patients, both of whom had reductions in sural SNAP amplitude, and one each had reductions in median and ulnar amplitudes (1). In a study of Taxol (135 to 350 mg/m^2) and cisplatin (75 mg/m^2) used in conjunction with G-CSF, Chaudhry and co-workers observed that sural SNAP amplitudes were reduced in 15 of 21 patients (51). The percentage reductions from pretreatment values ranged from 15 to 100% (mean, 50%). H-reflexes, which represent an electrophysiological correlate of ankle reflexes, appeared to be the most sensitive NCS parameter. Of 21 patients, 17 had either prolongation of latency or disappearance of the H-reflex following treatment with the Taxol-cisplatin + G-CSF regimen (51).

Nerve biopsies. Sural nerve biopsy findings have been reported in two patients. In one patient, in which the biopsy was performed several months after treatment, no disarray or aggregation of microtubules was noted in axons or Schwann cells (36). Thinly myelinated axons were also present that were interpreted as remyelination. However, axonal degeneration may also induce similar changes. In another report, a sural nerve biopsy from a symptomatic patient who received 19 courses of Taxol at 275 mg/m^2 over a period of 1 year revealed severe nerve fiber loss, axonal atrophy, and secondary demyelination (43). Based on these findings, it was concluded that a ganglionopathy (cell body disease) was a more likely mechanism for the toxic neuropathy caused by Taxol than either a distal axonopathy or a Schwann cell disorder.

Treatment. Treatment with amitriptyline has been found by some investigators, but not by others, to be useful in ameliorating residual neuropathic symptoms. However, narcotic analgesics appear to be more reliable at relieving clinically significant drug-induced dysesthesias (35,39,41). The availability of nerve growth factor, as well as other neuroprotective agents, such as ORG 2766 and WR 2721, also presents possible opportunities to study the feasibility of neuroprotection. Nerve growth factor, a neuronotrophic factor required for maintenance of sympathetic and dorsal root ganglion cells in culture, has been shown to attenuate the microtubule-disrupting and neurotoxic effects of Taxol in organotypic cultures (52). In a murine model of Taxol-induced neurotoxicity, co-administration of nerve growth factor and Taxol prevented changes indicative of Taxol-induced neurotoxicity that were observed when Taxol was administered without nerve growth factor, including decreases in dorsal root

ganglion content of the peptide neurotransmitter, substance P, elevated threshold to thermally induced pain, and diminished amplitude of the compound action potential in the caudal nerve (53).

Prognosis. Mild sensory symptoms have usually improved or resolved completely within several months after discontinuation of therapy. Areflexia has also been reported to resolve completely. However, some symptoms and deficits may persist for long periods after therapy, especially in patients who develop more severe neuropathies. For example, significant functional deficits have persisted for longer than 1 year in a diabetic patient who rapidly developed severe pansenory deficits after receiving Taxol (2,51).

Pathogenesis. The site of Taxol action and its pathogenesis is unclear. The clinical features would suggest that the toxic sensory neuropathy is caused by either an axonopathy or a neuronopathy. A model for the pathogenesis of Taxol-induced peripheral neurotoxicity is depicted in Table 2. Although Schwann cells are also known to be affected in vitro (21–25), there is no clear clinical evidence that a primary demyelination process is involved. In most patients, the distal symmetrical length-dependent affection, the predominant reduction of SNAP amplitude with relative preservation of conduction velocity, and the slow progressive evolution and reversibility after discontinuation of therapy all favor an axonopathy as the primary pathogenic mechanism. On the other hand, in some patients, especially those treated with higher doses, the simultaneous affection of lower and upper extremities, and occasionally of the face, the marked disproportionate loss of large fiber modalities, generalized areflexia, and poor recovery favor a cell body disease (dorsal root ganglia affection). Therefore, it is likely that Taxol induces both a sensory axonopathy and ganglionopathy, the latter occurring with higher single and cumulative doses, or in combinations with cisplatin.

Motor Neuropathy

Unlike sensory neuropathy, motor neuropathy is not a well-recognized neurotoxicity of Taxol. One reason for this may be that a mild distal weakness rarely affects function. Examination of 20 patients with Taxol-induced

sensory neuropathy revealed mild weakness of the distal extensor muscles in 16 of the subjects (51). NCS in these patients showed a reduction in peroneal-evoked amplitude. The degree of reduction ranged from 16 to 100% (mean, 61%) compared with baseline. The extent of reduction also correlated with the total cumulative dose of Taxol (2,51). In addition, Lipton et al. reported an absent peroneal motor evoked response in one patient treated with multiple courses of Taxol at 250 mg/m² (42). Sarosy et al. also reported a 49% reduction in peroneal amplitude with normal motor amplitude in median and ulnar nerves (1).

The distal symmetrical affection, the slow evolution with cumulative doses, the associated sensory neuropathy in most patients, and the NCS findings of reduced amplitude with normal latencies are all consistent with an axonopathy as the primary pathogenic process for the motor neuropathy. Interestingly, the mixed sensory and motor axonal neuropathy induced by Taxol closely resembles the neuropathy induced by the vinca alkaloid vincristine, another antimicrotubule agent (54).

Autonomic Neuropathy

In early phase I trials of Taxol administered over 6 hours, transient paralytic ileus was reported involving two diabetic patients who received Taxol at 250 mg/m² (36). Symptomatic orthostatic hypotension was also noted in two patients treated with Taxol, 250 to 275 mg/m², including one patient with diabetes mellitus (45). In addition, some of the cardiac rhythm disturbances that have been observed with Taxol, including bradyarrhythmias, atrioventricular conduction blocks, and ventricular arrhythmias, may represent manifestation of autonomic neuropathy or may represent true cardiac toxicity (55). Similar autonomic disturbances have also been reported with vincristine (54).

Myopathy and Myopathic Effects

Transient myalgias are commonly observed after treatment with moderate to high doses of Taxol administered over 6 to 24 hours (1,2,35–41,44,45). These symptoms generally occur 2 to 3 days after treatment and resolve within 5 to 6 days. Myalgias are usually mild and uncom-

Table 2. Pathogenesis model of Taxol-induced peripheral neurotoxicity*

Demyelination	Axonopathy	Ganglionopathy
1. Schwann cells affected in vitro.	1. Generally distal and length-dependent.	1. Simultaneous onset in upper and lower extremities.
2. Demyelinative effects occasionally seen on nerve conduction studies and biopsies.	2. Generally symmetrical.	2. Facial involvement.
—primary?	3. Reduced sensory and motor evoked amplitudes with normal conduction velocities.	3. Disproportionate loss of large fiber functions.
—secondary?	4. Slow evolution and reversibility.	4. Generalized areflexia.
	5. Ankle jerk reflexes reduced/absent. Other reflexes normal.	5. Poor recovery.
		6. Nerve conduction studies like axonopathy.

*Based on available clinical data, it is likely that Taxol induces both an axonopathy and ganglionopathy, the latter occurring with higher single doses and/or in combination with cisplatin.

mon at Taxol doses below 170 mg/m². However, most patients receiving doses ranging from 200 to 250 mg/m² experience myalgias that are mild to moderate in severity. Although severe myalgias requiring narcotics for palliation and dose reductions are occasionally noted at these doses, severe muscular complaints are generally experienced by patients receiving higher Taxol doses (>250 mg/m²) (2,41). The use of cisplatin in combination with Taxol does not appear to affect the severity of myalgias compared to single-agent Taxol at comparable doses. Large axial muscles, especially shoulder and paraspinal muscles, are frequently involved. Concurrent signs of inflammation and elevations in muscle enzymes such as creatine phosphokinase have not been observed (44). Collective experience at The Johns Hopkins Oncology Center has revealed minimal relief from and prevention of symptoms with the therapeutic or prophylactic use of nonsteroidal anti-inflammatory agents, and narcotics are usually administered prophylactically on days 2-5 post treatment. However, antihistamines recently have been reported to be very useful in preventing acute Taxol-induced myalgias (56).

A myopathy has been documented in four patients treated with high doses of Taxol (250 to 350 mg/m²) in combination with cisplatin (75 to 100 mg/m²) and G-CSF (51). These patients had new onsets of proximal muscular weakness affecting function. The weakness was greater in the lower extremities than in the upper extremities, and patients complained of difficulty with climbing stairs and rising from a low sitting position. EMG studies revealed myopathic motor unit potentials in all patients, and acid phosphatase staining of a muscle biopsy performed in the only patient with clinically significant myopathic complaints revealed dense staining of lysosomes suggesting a toxic myopathy (see section on Taxol-cisplatin [+ G-CSF]). This histochemical pattern resembled myopathies reported with colchicine. Lipton and co-workers also described a patient who developed progressive proximal muscle weakness involving both the upper and lower extremities while receiving 19 courses of Taxol as a single agent at doses ranging from 170 to 250 mg/m² (42). EMG studies also revealed myopathic findings. In this patient, the myopathic findings resolved and the weakness improved within several weeks following the discontinuation of Taxol. In addition, there have been several other reports of distal muscle weakness in patients receiving Taxol, including two patients with diabetes mellitus, who received multiple courses of Taxol (250 mg/m²) as single-agent therapy (35).

Central Nervous System Toxicity

Two episodes of possible central nervous system toxicity, as manifested by grand mal seizures, have also been noted during early single-agent trials (37,39). One patient with a history of seizures secondary to brain metastases had two grand mal seizures 45 minutes apart 2 hours after receiving Taxol at a dose of 250 mg/m² (37). A CT scan of the brain showed enlarging metastases and a postictal phenytoin blood level was subtherapeutic. The second pa-

tient with ovarian carcinoma and no history of brain metastases developed grand mal seizures 2 hours after the start of her first Taxol course (39). The infusion was discontinued and a neurologic evaluation was initiated. CT and magnetic resonance imaging of the brain, lumbar puncture, and an EEG were unremarkable, but major motor seizures reoccurred immediately after restarting Taxol. Because of the temporal relationship between drug administration and symptoms, the seizures were presumed to be related to Taxol. Interestingly, Taxol has not been detected postinfusion in the cerebrospinal fluid of leukemia patients receiving doses ranging from 250 to 390 mg/m², suggesting that there may be no or negligible penetration of Taxol into the central nervous system (40).

RISK FACTORS

Factors that may predispose patients to developing severe peripheral neurotoxicity during Taxol treatment are similar to those factors that predispose patients to other toxic neuropathies, including significant prior exposure to known neurotoxic agents and antecedent medical disorders that are also capable of inducing peripheral neurotoxicity, such as diabetes mellitus. Previous therapy with other neurotoxic chemotherapy agents was examined retrospectively in one phase I study as a risk factor for the development of peripheral neuropathy related to Taxol (35). In that study, 18 patients were treated with potentially neurotoxic doses of Taxol ranging from 170 to 265 mg/m² (6-hour infusion). Of the 11 patients in this group who previously received cisplatin or vinca alkaloids, nine developed symptomatic neurotoxicity. Seven patients received no prior therapy with neurotoxic agents, but five still developed neuropathic effects. McGuire et al. also reported that multiple courses (1 to 20) of Taxol induced either no or mild neuropathic symptoms in the majority of ovarian cancer patients who had been heavily pretreated with platinum-based drug regimens (36). However, the extent of prior chemotherapy and neutropenia limited Taxol doses during most courses in that trial to 110 to 170 mg/m². Similarly, patients with refractory ovarian cancers who were heavily pretreated with platinum-based therapies developed no or minimal neurotoxicity after receiving multiple courses with higher doses of Taxol (170 to 250 mg/m²) combined with G-CSF, but severe neurotoxicity precluded therapy at Taxol doses above 250 mg/m² (1). Interestingly, all patients who developed severe neurotoxicity at doses above 250 mg/m² developed a clinically significant peripheral neuropathy while they received their prior cisplatin-based anticancer regimen, which was either grade 0 or 1 at the time of Taxol initiation. Patients with histories of substantial prior ethanol use also appear predisposed to developing clinically significant peripheral neuropathies during Taxol treatment. This has been particularly noted during phase I studies of the Taxol-cisplatin combination regimen (2,45). In these studies, patients with a history of excessive prior ethanol use, especially those with mild peripheral neuropathies related

to ethanol, were more likely to develop a peripheral neuropathy that was more severe compared with neurotoxic manifestations experienced by patients without a history of excessive prior ethanol use (see section on neurotoxicity: Taxol-based combination chemotherapy).

Patients with long-standing diabetes mellitus have also appeared to be more prone to developing severe neurotoxicity while receiving Taxol either as a single agent or in combination with cisplatin (35). In addition to developing the more common neurosensory manifestations, these patients have developed other less common manifestations that have occasionally been severe, including motor effects, paralytic ileus, and a toxic myopathy (see "Clinical Manifestations and Neurotoxicity: Taxol-based Combinations" section).

RELATING PHARMACOLOGIC PARAMETERS TO NEUROTOXICITY

A limited number of early phase I studies sought to identify relationships between Taxol-induced neurotoxicity and several pharmacologic parameters. During a phase I trial of Taxol administered on a 6-hour infusion schedule, a relationship between neuropathy and Taxol AUC was identified, with neurotoxicity only appearing at AUC values greater than $25 \mu\text{g} \times \text{h/mL}$ (37). Similarly, neurotoxicity was demonstrated to roughly correlate ($r = 0.54$, $P < 0.01$) with steady-state Taxol concentrations in a phase I trial of Taxol (135 to 350 mg/m^2) combined with cisplatin (75 to 100 mg/m^2) and G-CSF; however, the correlation between the grade of neurotoxicity and Taxol dose was similar ($r = 0.56$, $P < 0.01$) (2).

SUMMARY

Even though hematopoietic growth factors have reduced the duration and severity of clinically significant Taxol-induced neutropenia, neuromuscular toxicity limits the use of high single and cumulative doses of Taxol as a single agent and in combination with cisplatin. To date, the principal neuromuscular effects that have been documented with Taxol include a polyneuropathy, acute myalgias, and a myopathy. The majority of historical, physical, and NCS findings suggest that single-agent Taxol induces either a primary axonopathy, ganglionopathy, or both. While sensory symptoms predominate, motor involvement is usually demonstrable clinically and by NCS at relevant Taxol doses. Severe sensory loss, generalized weakness, myopathy, and autonomic dysfunction (e.g., paralytic ileus, orthostatic hypotension) are rare and usually only evident in patients treated with relatively high, albeit clinically relevant, doses or those who may be generally predisposed to developing toxic neuropathies. Currently, there is insufficient information available about the relationship between Taxol dose and antitumor activity. Therefore, it is not possible to gauge the relative clinical benefits of higher doses of Taxol ($\geq 200 \text{ mg/m}^2$). It is possible that higher doses of Taxol, such as doses requir-

ing the co-administration of G-CSF, may lead to more severe neurotoxicity and yet equivalent antitumor activity when compared to lower doses. While clinical studies addressing dose-response issues are in progress, available data suggest that caution should be used and possibly dose modifications considered for patients who may be at high risk for developing severe neuromuscular toxicity, such as patients with prior histories of excessive ethanol use and antecedent medical disorders (e.g., diabetes mellitus). Additionally, clinical research efforts should be focused on the early identification of patients who are likely to develop severe neuromuscular complications with subsequent dosing, perhaps by using NCS, quantitative sensory testing, or limited, selective neurological examinations. Research efforts should also be addressing the feasibility of neuroprotection with agents such as nerve growth factor. As with the vinca alkaloids, structure-function studies may also be vital to develop taxane analogues with superior therapeutic indices.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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A Reassessment of Cardiac Toxicity Associated with Taxol

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Cardiac toxicity was first noted in patients receiving Taxol during continuous cardiac monitoring, which was performed because of the high incidence of serious hypersensitivity reactions noted early in phase I trials. After cardiac events were documented, patients with cardiac disease and those on medications known to alter cardiac conduction were excluded from most trials. The cardiac events reported with Taxol from the initiation of NCI-sponsored clinical trials through August 1992 are summarized. Adverse cardiac events were reviewed in four clinical databases: 1) the Cancer Therapy Evaluation Program's Adverse Drug Reaction database following treatment of more than 3400 patients; 2) all cardiac toxicities in patients on GOG-111 who were randomized to cisplatin plus either Taxol or cyclophosphamide; 3) cardiac toxicity in 198 patients who received 618 courses of Taxol with or without cisplatin during continuous cardiac monitoring; and 4) cardiac toxicities reported for the first 696 patients on NCI TRC-9103 for ovarian cancer. Published reports of studies of taxine's cardiac effects, and of cardiac toxicity associated with yew poisoning, Cremophor EL, and H₁ and H₂ antagonists, are also reviewed. In patients without significant cardiac risk factors, asymptomatic sinus bradycardia is frequent (approximately 30%). Heart block and conduction abnormalities occur infrequently and are often asymptomatic. The casual relationship of Taxol to atrial and ventricular arrhythmias and cardiac ischemia is less clear because many patients had other conditions known to be associated with cardiac events. Nevertheless, the incidence of serious cardiac events was low. Routine cardiac monitoring is not required for patients without risk factors. There are, however, insufficient data to make treatment recommendations for patients with cardiac disease and those taking medications that alter cardiac conduction. To maximize patient safety and the clinical database, physicians who administer Taxol should continue to be alert to potential cardiac toxicities associated with Taxol. [Monogr Natl Cancer Inst 15:117-130, 1993].

BACKGROUND

During the clinical development of Taxol¹ particular attention was paid to its cardiac effects, even though standard preclinical toxicology evaluation revealed no histological evidence of cardiac toxicity (1). The only cardiovascular effects, hypotension and shock, occurred during

rapid Taxol administration to dogs and were consistent with the known histamine release effects of the Cremophor EL vehicle in which Taxol is formulated (1,2).

Concern arose when cardiac effects were detected in patients during a phase II Taxol trial at the Johns Hopkins Oncology Center (JHOC) (3). Continuous cardiac monitoring, not usually performed during development of anticancer drugs by the National Cancer Institute (NCI), was routinely performed during the study because of the high incidence of major hypersensitivity reactions during early phase I trials. With the simultaneous adoption of a routine premedication regimen and prolongation of the infusion time to 24 hours, the incidence of major hypersensitivity reactions declined; however, cardiac arrhythmias were documented. Asymptomatic bradycardia (30-50 beats/min) was noted during one or more Taxol infusions in 29% of 45 monitored patients (3). Two patients also developed significant cardiac conduction abnormalities, including first-, second-, and third-degree atrioventricular (AV) block, leading to permanent pacemaker implantation in one patient (3). In both patients, the AV conduction abnormalities were transient and resolved 4 hours to several days following Taxol treatment. Both patients continued treatment with Taxol without complications (3,4). The patient with a pacemaker developed bradycardia during each treatment, resulting in pacemaker capture.

In November 1987, after documentation of intermittent complete heart block in the first patient at JHOC, the Cancer Therapy Evaluation Program (CTEP) of the NCI sent a warning letter to notify investigators who were treating patients on Taxol trials. In September 1990, a second warning letter was sent when brief runs of asymptomatic ventricular tachycardia (VT) were noted in several patients on a phase I trial of Taxol and cisplatin, also performed with continuous cardiac monitoring, at JHOC (4). Brief runs (3-72 beats) of asymptomatic VT were subsequently reported in 5 of 44 patients (11%) on that trial. In 1991, Rowinsky et al. reviewed the cardiac events in the two trials previously cited (3,4) along with those in two other clinical trials. They reported a variety of adverse cardiac events, including sinus bradycardia, AV conduction disturbances, left bundle branch block, ventricular premature contractions (VPCs), VT, and manifestations of cardiac ischemia (including one patient with myocardial infarction), which were observed in 5% of 140 patients (5). These disturbances, which for the most part were reversible and rarely resulted in serious sequelae, may have been multifactorial in etiology, with other drugs

*See "Notes" section following "References."

and underlying heart disease recognized as possible contributing factors (5).

After adverse cardiac events were reported, patients with potential cardiac risk factors were excluded from many Taxol trials. Patients who would not be expected to tolerate bradycardia, including those with a history of angina or congestive heart failure or those who had suffered a myocardial infarction within 6 months, were generally excluded. In addition, patients with arrhythmias and those taking medications known to alter cardiac conduction, including digoxin, beta-adrenergic blockers, and calcium channel blockers, were ineligible. Because cancer most frequently affects the elderly in whom cardiac conditions and the use of cardioactive medications are common, these criteria exclude many patients who might benefit from Taxol.

The purpose of this report is to summarize and evaluate information from four databases on adverse cardiac events, including brady- and tachyarrhythmias, intraventricular conduction disturbances, myocardial infarction, and cardiac ischemia. These will be reviewed in the context of existing information about the frequency of underlying cardiac arrhythmias in similar patient populations and adverse cardiac events associated with the medications used routinely with Taxol to decrease the incidence of severe anaphylactic reactions. The relationship of Taxol therapy to the adverse cardiac event and the risk to patients will be assessed. In addition, mechanisms underlying the abnormalities will be discussed.

Cardiac Toxicity Associated with Yew Poisonings and Taxines

The poisonous properties of yew have been recognized at least since the fourth century (6). Poisonings in humans were recorded as early as the 18th century, when many women died from ingesting yew as an abortifacient, and lawsuits have resulted when animals were poisoned from negligent disposal of yew clippings (7).

Signs and symptoms of systemic poisoning appear soon after ingestion and include mydriasis, dizziness, nausea with or without vomiting, abdominal cramping, loss of consciousness, tachycardia, cardiac arrhythmias, and hypotension (7). Respiratory difficulty and convulsions may also be seen. Death due to cardiac arrest, respiratory failure, or circulatory collapse has been reported.

With the exception of the fruit, all parts of the plant are poisonous (7). Because the seed coat resists digestion, the seeds are toxic only if they are chewed. The toxic component is poorly characterized. Taxine, which was first isolated in 1956, comprises the alkaloid fraction of the plant, and this fraction contains at least 10 separate alkaloids, most of which are also incompletely characterized. The major fully characterized taxines are taxine A and B. Taxine B has cardiac effects; taxine A does not.

The individual cardiotoxic components of the alkaloid fraction "taxine" (for example, taxine B) possess the taxane ring system and some of the substituent positions in common with Taxol (Fig. 1). The nitrogen-containing side chain of the taxines, however, believed important for

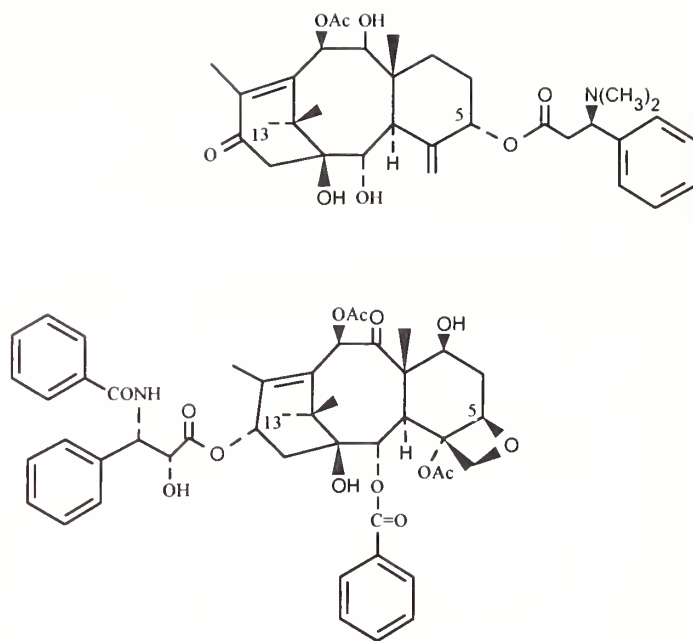


Fig. 1. Structures of taxine B (top) and Taxol.

the cardiotoxic activity, extends from the 5-position on the C ring of the taxane skeleton, while the main side chain of Taxol extends from the 13-position of the A ring. The A, B, and C rings of the taxane skeleton form an inverted "U" shape, however, and positions 5 and 13 are quite close in space as seen in the x-ray structure of Taxotere² (8). Substituents at these positions could have partial overlap of binding sites, thus potentially explaining the cardiotoxicity of Taxol.

Lowe investigated the effects of a taxine preparation on himself and documented bradycardia with increased pulse pressure (6). Four cases of self-poisoning occurred when prisoners drank an extract of yew leaves and bark (9). One was found dead in his cell, and another died during transport to the hospital. A third, who was unconscious, was resuscitated after developing ventricular fibrillations (VF). This patient developed VT, recurrent episodes of VF requiring defibrillation, a short period of asystole, then rapid ventricular rhythm and another episode of VF. After defibrillation, he developed a transient but hemodynamically stable ventricular rhythm and then normal sinus rhythm. The patient had excessive diuresis and hypokalemia requiring potassium supplementation. Lidocaine and steroids were also administered, with initial improvement over the first 24 hours. He later developed ventilation disturbances and supraventricular tachycardia, however, possibly due to hypoxia. The patient continued to deteriorate. On day 3 he developed hypotension and intermittent bradycardia to 40 beats/min or less. Although he responded to dopamine and atropine, he died on day 4 in asystole, which was refractory to medications. The fourth prisoner was admitted to the hospital with sinus bradycardia at a rate of 45 beats/min. After intravenous

atropine, his rate quickly normalized for several hours. Recurrence of bradycardia led to a pacemaker implantation. Short bouts of ventricular extrasystoles were treated with repeat boluses of lidocaine. This patient also had excessive diuresis and hypokalemia requiring potassium supplementation. He recovered and was discharged 10 days later.

In another case of lethal intoxication, a patient became dizzy 1 hour after ingesting yew leaves (10). This patient also developed nausea, diffuse abdominal pain, unconsciousness, tachycardia, and brief episodes of ventricular flutter, slow pulse, respiratory arrest, cardiac standstill, and death. Electrocardiogram (ECG) showed intraventricular conduction delay (0.24 seconds) with a nonspecific pattern, and, surprisingly, P waves were absent.

Animal Experiments

Rabbits receiving bolus injections of taxine for LD₅₀ determination developed a prolonged PR interval and a prolonged QRS complex (6). After a short period with occasional missed beats, the heart rate decreased to about 50% of control. In rabbits that recovered, the slow rate lasted approximately 20 minutes, after which effects resolved in reverse order from their development. Bradycardia from taxines has also been documented in mice and guinea pigs (7).

Studies with taxine in isolated perfused frog and rabbit hearts demonstrated slowed beating and subsequent development of 2:1 heart block and then complete heart block (6). Ventricular asystole was followed by atrial and sinus node quiescence, suggesting that the bradycardia was due to depression of conduction, although inhibition of automaticity could not be excluded. Sectioning of vagi, atropine, digoxin, and adrenaline appeared to produce no chronotropic effects (6). Taxines appear to have similar effects in many different animal species (6,11,12). Tolerance has been described in rabbits, guinea pigs, and cattle (6).

In a study of intoxication in dogs, ECG abnormalities developed in three stages (13). Progressive prolongation of QRS duration during sinus rhythm suggested intraventricular conduction impairment. QRS complexes that were initially uniform ultimately became polymorphic, and after 33 minutes the animals developed VF and died. In another study, the effects of an alkaloid mixture of yew (*Taxus baccata*) converted to sulphate salt were determined on the isolated frog heart (14). Both atrial and ventricular rates were slowed in a dose-dependent manner; however, the rate-depressing effect was more prominent on the ventricle, indicating that atrioventricular conduction is more sensitive to the drug. These effects of the drug on the heart were only partially reversible on washing, and calcium-rich solutions did not alter the atrial rate but significantly increased the ventricular rate.

In another study in enzymatically isolated guinea pig ventricular cells, high concentrations of taxine inhibited both sodium and calcium currents (15). Whether these effects on the calcium current are responsible for the bradyarrhythmic effect seen in vivo is unclear.

Experimental data with taxines in various animal species and reports of yew poisonings from the toxicology literature strongly suggest that Taxol causes cardiac conduction abnormalities and bradycardia. The structural similarities between Taxol and taxine B, which is a known cardiac toxin, also support this conclusion.

Cardiac Arrhythmias Before Cancer Chemotherapy Administration

The number of cardiac events detected in early clinical trials of new agents, such as Taxol, may, in part, be related to the type and frequency of cardiac monitoring. For example, pretreatment Holter monitoring prior to any Taxol therapy detected ectopy in 86% of 22 patients [(16) and Gibbs H, Holmes F, unpublished data]. Twenty-seven percent of these patients had either nonsustained supraventricular tachycardia or complex ventricular ectopy on the pretreatment Holter. Had pretreatment evaluation not been done, these abnormalities might have been attributed incorrectly to the Taxol and doxorubicin that they subsequently received.

In another study, 36 patients underwent 24-hour Holter monitoring prior to and following administration of phase I chemotherapy (17). Sixty-four percent had preexisting non-drug-related ventricular and supraventricular arrhythmias. Eight-four percent of arrhythmias detected by Holter monitoring were not detected by a baseline electrocardiogram or a 1-minute rhythm strip. Thirty-six percent of the arrhythmias detected by the Holter monitor were considered potentially serious enough to warrant treatment.

In another study of 19 patients who had continuous ECG recordings prior to doxorubicin administration, 18 had supraventricular extrasystoles, 11 had 173 runs of supraventricular tachycardia, 17 had extrasystoles (including bigeminy and paired beats), and 4 had ventricular tachycardia (mean, 22 beats; range, 12–34) (18).

These data confirm the importance of documenting preexisting arrhythmias that might otherwise be incorrectly attributed to an investigational treatment.

Adverse Cardiac Events Associated with the Cremophor Formulation and the Premedication Regimen

The Cremophor EL vehicle in which Taxol is formulated is known to induce histamine release, which may stimulate H₁ and H₂ receptors. Stimulation of these receptors in cardiac tissue can increase myocardial oxygen demand and produce coronary vasoconstriction (H₁) and chronotropic effects (H₂) (5,19–25). Animal studies indicate that stimulation of H₁ receptors results in prolonged AV conduction, possible depression of conduction in Purkinje tissue, myocardial cell injury, and ventricular arrhythmias (19,23,24). Absence of evidence for systemic histamine release does not rule out its pathophysiologic role, since histamine is released by the heart in response to various drugs (19,20). Selective activation of histamine receptors in cardiac tissue might explain the bradycardia, AV conduction prolongation, bundle branch block,

ventricular irritability, and perhaps even cardiac ischemia that have been reported in association with Taxol treatment (5).

Cardiovascular reactions, including hypotension, have been reported in patients treated with some other drugs formulated in Cremophor EL, for example, miconazole (26-29), teniposide (30), and cyclosporin (29). Ventricular tachycardia and cardiac arrests have been reported with miconazole (26,27). Although cardiac arrhythmias are rarely reported, patients who receive these drugs do not routinely undergo cardiac monitoring. Notably, however, Taxol is formulated with the highest concentration of Cremophor EL per dose of all drugs in clinical use (1).

Cardiac rate and rhythm abnormalities, especially bradyarrhythmias, occur following administration of H₂ antagonists (31), cimetidine (26,27,29,32,33), ranitidine (29), and famotidine (29). Patients with advanced age, severe systemic illness, and renal dysfunction experienced some of the most severe episodes, most of which occurred immediately after administration of the H₂ antagonists (34,35). In contrast, many of the cardiac disturbances associated with Taxol and reported by Rowinsky et al. (5) appeared later during the infusion. These were usually self-limited or resolved soon after discontinuation of the Taxol infusion. These findings suggest that the disturbances reported were more likely related to Taxol than to H₂ antagonists.

Hypotension, palpitations, tachycardia, and extrasystoles have also been reported in association with diphenhydramine (26,29,32), which is also part of the routine premedication regimen adopted for Taxol.

MATERIALS AND METHODS

By August 1992, more than 3400 patients had been treated with Taxol in the United States. Information on adverse cardiac events associated with Taxol is available from a variety of sources, including first, the CTEP Adverse Drug Reaction (ADR) database; second, toxicity data from both arms of study GOG-111, in which previously untreated patients with suboptimally debulked stages III and IV ovarian cancer were randomized to cisplatin plus either Taxol or cyclophosphamide; third, toxicity data from more than 600 refractory ovarian cancer patients who were treated at 39 NCI-designated Comprehensive Cancer Centers on the NCI Treatment Referral Center (TRC) protocol TRC-9103; and fourth, information obtained from five clinical trials in which 154 patients who were treated with Taxol alone and 44 patients who received the combination of Taxol and cisplatin underwent continuous cardiac monitoring during Taxol administration. The information obtained from these sources varies because of differences in the type and frequency of cardiac monitoring and the requirements for toxicity reporting. Because all grade 4 and 5 adverse events (life-threatening reactions and deaths) occurring in NCI-sponsored clinical trials must be reported to CTEP, these databases are not mutually exclusive. NCI's Common

Toxicity Criteria were used. The criteria for cardiac events are listed in Table 1.

For phase II and III clinical trials, CTEP requires written reports of grade 4 and 5 toxicities (except myelosuppression) and all previously unknown toxicities within 10 days of the event. Although known grade 2 and grade 3 toxicities are sometimes reported, these data are incomplete until submission of yearly study summaries. For the CTEP ADR data summarized here, only data for grade 4 (life-threatening) and grade 5 (death) toxicities can be considered complete.

All grades of cardiac toxicity were available for patients treated on GOG-111 and TRC-9103 and for 198 patients who underwent continuous cardiac monitoring during Taxol therapy in five different clinical trials.

RESULTS

CTEP ADR Database

In patients enrolled in Taxol studies, the incidence of all adverse grade 4 and 5 cardiac events reported to CTEP was 0.5%. A number of events that for various reasons appear not to be directly related to the administration of the drug are included.

Ventricular arrhythmias. Seven cases of nonsustained ventricular tachycardia (NSVT) (patients 1 to 7) have been reported. All occurred in patients undergoing continuous cardiac monitoring during Taxol infusion (Table 2), and five were described previously by Rowinsky et al. (4,5). None of these patients had cardiac symptoms prior to entering the Taxol clinical trials, and none had symptoms in association with these episodes. The median number of beats in the runs of NSVT was five, six patients had six or fewer beats, and one patient had 72 beats. Most of the patients who had VT also had VPCs, and some had bigeminy or trigeminy. For all seven patients, the median time to occurrence of VT was 12 hours into the Taxol infusion (range 1-24 hours). There was no evidence of electrolyte disturbance in any of these seven patients.

Of these patients, six were undergoing therapy with a combination of Taxol and cisplatin. Because Taxol was administered before cisplatin in three of the four episodes initially reported by Rowinsky et al., the observed cardiac toxicity was attributed to Taxol (5). It is interesting, however, that all but one episode of VT reported here occurred during the second cycle or later cycles of therapy. Furthermore, transient ECG changes have been reported in patients treated with cisplatin (36). Patients who receive cisplatin do not usually undergo cardiac monitoring, however; therefore, assessment of the potential role of cisplatin in arrhythmias that followed combination treatment is not possible.

Interestingly, NSVT was documented in only one patient (patient 7) who received Taxol alone. This patient had a five-beat run of NSVT during her second course but subsequently received 15 monitored courses of Taxol without recurrence of NSVT. This patient also experienced intermittent 2:1 heart block during most of her courses.

Table 1. NCI common toxicity criteria for cardiac events*

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac dysrhythmias	None	Asymptomatic, transient, requiring no therapy	Recurrent or persistent, no therapy required	Requires treatment	Requires monitoring; or hypotension, or ventricular tachycardia, or fibrillation
Cardiac function	None	Asymptomatic, decline of resting ejection fraction by less than 20% of baseline value	Asymptomatic, decline of resting ejection fraction by more than 20% of baseline value	Mild CHF, [†] responsive to therapy	Severe or refractory CHF
Cardiac ischemia	None	Nonspecific T-wave flattening	Asymptomatic, ST and T-wave changes suggesting ischemia	Angina without evidence for infarction	Acute myocardial infarction
Hypertension	None or no change	Asymptomatic, transient increase by greater than 20 mm Hg (D) [§] or to >150/100 if previously WNL. No treatment required	Recurrent or persistent increase by greater than 20 mm Hg (D) or to >150/100 if previously WNL. No treatment required	Requires therapy	Hypertensive crisis
Hypotension	None or no change	Changes requiring no therapy (including transient orthostatic hypotension)	Requires fluid replacement or other therapy but not hospitalization	Requires therapy and hospitalization; resolves within 48 h of stopping the agent	Requires therapy and hospitalization for >48 h after stopping the agent

*Grade 5 toxicity = death on study.

[†] CHF = congestive heart failure.

[‡]WNL = within normal limits.

[§]D = diastolic.

Patient 1 was treated with lidocaine, and the Taxol infusion was discontinued. The infusion was interrupted for two patients. Four patients completed the course of treatment as planned, and no significant sequelae occurred in any of these patients.

The one case of VF occurred in patient 8, who developed life-threatening hypokalemia secondary to severe diarrhea following treatment with the combination of Taxol and doxorubicin. On day 12 of her third cycle, she developed VF and cardiac arrest during attempts at vigorous electrolyte repletion. The patient was resuscitated.

The ninth patient had bigeminy documented on an ECG prior to initiating Taxol treatment and was treated in violation of the protocol eligibility criteria. Six days following treatment she was readmitted to the hospital with dizziness and mental status changes. Her physician ascribed her death to a cardiac arrhythmia, but there was no documentation of the patient's rhythm on readmission to the hospital or of a cardiac evaluation to determine the etiology of the preexisting arrhythmia and exclude underlying cardiac disease. Although one cannot exclude the possibility that Taxol exacerbated a preexisting abnormality, it is also possible that the patient's death was due to an antecedent medical problem that was not evaluated or treated. The cause of death is unknown.

To date, the incidence of VT and VF reported to CTEP is 0.26%.

Atrial arrhythmias. Reports of eight patients with atrial arrhythmias have been submitted to CTEP (Table 3). Five of these patients developed atrial fibrillation, one developed atrial fibrillation/flutter, and two developed supraventricular tachycardias (SVT). Grade 3 toxicity (requiring treatment) was reported in four patients, and grade 4 toxicity (life threatening or resulting in continuous cardiac monitoring) in four patients. Six of these patients (75%) had no cardiac symptoms associated with the arrhythmia.

Three of these patients had a prior history of atrial fibrillation, and one had sinus tachycardia prior to the initiation of Taxol. Other potential risk factors included rheumatic heart disease (in a patient with a prior history of atrial fibrillation), infection and fever, asthma, possible pulmonary embolus, and hypertension. Atrial arrhythmias were documented at a median course of 1.5 (range 1–7) and at a median time of 24 hours after the initiation of the Taxol infusion (range, 2.5 hours to 6 days). The arrhythmia was documented during the Taxol infusion in only four of the patients.

The incidence of significant atrial arrhythmias (atrial fibrillation, flutter, SVT) reported to CTEP is 0.24%.

Heart block. Heart block has been reported in only four patients, all in the group of 198 patients who underwent routine cardiac monitoring (see "Discussion"). These patients, two of whom have been described

Table 2. Ventricular arrhythmias*

Patient no.	Arrhythmia	Taxol dose mg/m ² /other chemotherapy	Symptoms	Course	Time into infusion	Toxicity grade	Duration of reaction	Drug alteration	Treatment required	Resolution reaction	Retreatment results	Comments
1†	NSVT	170/cisplatin	No	2	5 h VT 72 beat (20 sec) 13 h-VT 3 beats	3	Brief	Discontinued	Lidocaine	Recovered	NI	Cisplatin first then Taxol. Holter off Taxol: VPCs 3-VT: 3-6 beat runs (Clonidine pretreatment for hypertension).
2†	NSVT	170/cisplatin	No	3	12 h-VT 6 beats multifocal VPC, bigeminy	1	Brief	Interrupted	None	Recovered	Only VPC noted on retreatment	Course 4: VPC only. VPCs noted on first two courses. Holter off Taxol (glyburide, nifedipine pretreatment for diabetes mellitus, VPCs).
3†	NSVT	135/cisplatin	No	2	24 h-VT 4 beats	1	Brief	Interrupted	None	Recovered	No sequelae	Holter off Taxol: rare VPCs.
4†	NSVT	170/cisplatin	No	2	22 h-VT 3 beats 18 h VT 4 beats	1	Brief	None	None	Recovered	Five courses without problems	Sixth course left bundle branch block; resolved when Taxol discontinued.
5†	NSVT	170/cisplatin	No	1	5 beats VT 10/min, bigeminy, VPCs quadrigeminy	1	4 days	None	NI	Recovered	NI	Holter off Taxol: normal.
6	NSVT	135/cisplatin	No	4	12 h-VT 4 beats	2	NI	None	None	Recovered	NI	Three prior courses tolerated well.
7	NSVT bigeminy	250	No	2	11 h-VT 5 beats, VPCs, bigeminy	1	Brief	None	None	Recovered	Multiple courses subsequently	No recurrence of NSVT during 15 subsequent cycles.
8	VF	160/doxorubicin	Yes	3	Day 12	4	Brief	N/A	Defibrillation; recovered	NA	NA	Life-threatening hypokalemia due to diarrhea (Clonidine pretreatment for hypertension).
9	Undocumented arrhythmia	135/cisplatin	?	1	Day 6	5	NI	None	NI	Death	NA	Protocol violation. Bigeminy pretreatment, etiology unknown. Patient readmitted day 6 with dizziness, mental status change and died in hospital. Cause of death undetermined.

*NI = No information; NA = Not applicable.

†Previously reported in literature (5).

‡Infusion stopped at 12 h 2° LBBB; see entry in Table 5.

Table 3. Atrial arrhythmias

Patient No.	Arrhythmia	Taxol dose, mg/m ² /other chemotherapy	Symptoms	History (medications)	Courses	Time into infusion	Toxicity grade	Duration of reaction	Drug alteration	Treatment required	Resolution reaction	Retreatment results	Comments
10	A fib*/140	200	No	Hypertension (Aldomet, Dyazide)	5	24 h	3	1 d	None	Digoxin	Under treatment	NI	Discharged on digoxin. Echocardiogram: LVH.
11	SVT/160	135/cisplatin	No	Smoker (60 pack-years)	1	6 h	4	NI	Discontinued	Verapamil, Digoxin, Propranolol	Under treatment	NI	
12	A fib	135/cisplatin	No	NI	2	Post-treatment	3	NI	None	Digoxin	Recovered	NI	Admitted for infection: Irregular pulse. ECG-A fib.
13	A fib	250	Yes	Asthma, hypertension (Captopril, Minipres, Corgard)	1	2.5 h	4	1 d	Discontinued	O ₂ , Verapamil, Morphine, Digoxin	Recovered	NI	Dizziness, dyspnea, diaphoresis, shoulder pain, decreased breath sounds. Required O ₂ .
14	A fib/150	250	No	Rheumatic heart disease with prior A fib	7	48 h post-treatment	4	1 d	None	Digoxin	Recovered	Subsequent treatment without difficulty	24 h after Taxol: 3-min episode of nausea, sweating. ECG: rare PACs. Ventilation perfusion scan: intermediate probability of pulmonary embolus.
15	A fib	135	No	Post-anesthesia/A fib, 1°AV block	3	3 d post-treatment	3	NI	Discontinued	Digoxin	NI	NI	Admitted to hospital for abdominal pain, fever, irregular pulse. Clostridium sepsis. Echocardiogram: Small pericardial effusion.
16	A fib/flutter/120	200/cisplatin, cyclophosphamide	No	Prior A fib	1	During infusion	3	NI	None	Digoxin	On therapy	NI	
17	SVT	250	Yes	NI	1	6 d post-treatment	4	NI	NI	Neosynephrine, Verapamil, Digoxin, Cardioversion	Under treatment	NI	Had tachycardia before and after Taxol.

*A fib = Atrial fibrillation.

†NI = No information.

previously in the literature (3,5), are included in Table 4.

Three of these patients had advanced AV conduction disturbances. Of these patients, only one was symptomatic and only intermittently. Three patients underwent cardiac pacing (one with a permanent pacemaker). One of these (patient 7), who received 17 courses of Taxol, had asymptomatic advanced heart block with each course and was managed with prophylactic temporary transvenous pacing. Another (patient 19) had asymptomatic advanced heart block with her first course of Taxol. She underwent prophylactic pacing for her next three courses but had no recurrence of advanced heart block. Prophylactic pacing was not used for subsequent courses, although she continued to have central venous lines placed for vascular access in the event a pacemaker was required.

All four patients continued with therapy. There was no clinical or ECG evidence of cumulative cardiac toxicity. Holter monitoring between cycles revealed no evidence of heart block. No relationship between occurrence of heart block and dose or duration of treatment was apparent.

The incidence of heart block in the CTEP ADR database is 0.11%.

Myocardial infarction and ischemia. Seven patients developed myocardial infarction during and up to 14 days following Taxol therapy, four patients developed cardiac ischemia, and one developed nonspecific ECG abnormalities (Table 5). Most of these patients had known cardiac risk factors including hypertension (five patients), coronary artery disease (three), coronary artery bypass grafts (two), and previous myocardial infarction. Review of the records indicated that pretreatment alteration or omission of cardiac medications may have contributed to the cardiac events that occurred in two of these patients. Three of these patients died, and coronary artery disease was documented at autopsy for each.

Following administration of epinephrine for an anaphylactic reaction to Taxol, one patient developed ECG changes consistent with a possible myocardial infarction without cardiac enzyme abnormalities. This adverse event was indirectly related to Taxol. Another patient with a history of hypertension and diabetes mellitus was noted to have new onset of left posterior hemiblock (LPHB) and ECG changes consistent with a possible silent inferior myocardial infarction prior to her fifth course of Taxol. She completed her sixth course as planned. This event may have been related to Taxol (particularly in view of the LPHB), but silent myocardial infarction due to coronary artery disease in a diabetic cannot be excluded.

The incidence of grade 4 and 5 cardiac ischemic events reported to CTEP is 0.29%.

Other possible cardiac effects. Sinus bradycardia has been reported in 29% of patients undergoing routine continuous cardiac monitoring (3). The incidence of sinus bradycardia does not vary as a function of cycle (Cunnion R, Reed E, personal communication). In addition, clinically insignificant and nonsustained first-degree heart block was noted in 22 of 89 patients (25%) who began treatment with a normal PR interval (Cunnion R, Reed

E, personal communication). Bigeminy, trigeminy, increased VPCs, and chest pain rarely have been noted during Taxol infusions (5). Atypical chest and abdominal pains have also been reported in conjunction with symptoms associated with hypersensitivity reactions (hypotension, bronchospasm, and urticaria).

Syncope and hypotension in association with decreased oral intake have been reported in three patients (5). Prolonged cardiac monitoring and ECGs revealed no abnormalities, and Taxol was readministered. Hypertension requiring therapy has been reported in three patients, including one child who had received two extra doses of dexamethasone and a patient with a history of hypertension who took no antihypertensive medication.

In addition, some sudden deaths attributed to progressive disease and extensive tumor were reported; however, the mechanism of death was never established. In view of what is known about yew poisonings and the cardiac effects of taxines, one cannot exclude the possibility that some of these deaths were due to sudden arrhythmias resulting from Taxol therapy.

Adverse Cardiac Events in a Randomized Trial of Cisplatin Plus Either Taxol or Cyclophosphamide: GOG-111

As noted previously, a major limitation in determining the relationship of Taxol to cardiac events is the lack of information on cardiac risk factors, such as preexisting arrhythmias in the treated population. In the case of cardiac arrhythmias, the optimal way to obtain such data would be to perform continuous cardiac monitoring before and during therapy in comparable patients randomized to either Taxol or another treatment. Efforts are being made to obtain such data. A less direct and less optimal assessment can be made by comparing adverse cardiac events reported in patients who did not undergo continuous cardiac monitoring but who were randomized to one of two treatment regimens, either with or without Taxol.

Between April 1990 and March 1992, 410 patients with suboptimally debulked stages 3 and 4 ovarian cancer participating in GOG-111 were randomized to receive cisplatin 75 mg/m² with either Taxol 135 mg/m² or cyclophosphamide 750 mg/m². To meet cardiac eligibility criteria, patients could have no prior history of arrhythmias nor could they be taking medications for arrhythmias. Of note, patients taking calcium channel blockers for other indications such as hypertension were not excluded. An ECG was required prior to the first cycle of Taxol. The protocol required that Taxol be discontinued for AV nodal block. No modifications were required for asymptomatic bradycardia.

Cardiac toxicities of grade 2 or more were reported only in the Taxol arm. Six of 174 patients (3.4%) had grade 2 or worse toxicity (Table 6). Life-threatening toxicity was, however, limited to one patient, who died from a myocardial infarction that occurred 7 days after her first Taxol treatment. This patient (patient 22), who had autopsy documentation of coronary artery disease, was dis-

Table 4. Conduction abnormalities

Patient no.	Arrhythmia	Taxol dose, mg/m ² /other chemotherapy	Symptoms	Course	Time into infusion, h	Toxicity grade	Duration of reaction, h	Drug alteration	Treatment required	Resolution of reaction	Sequelae	Retreatment results
AV block												
18*	Bradycardia, Mobitz I & II, 2:1, third-degree HB [†] ; 7 s asystole	135	No	2	8, 16	4	48	Interrupted	Pacemaker	Recovered. Pacing only during and briefly following Taxol	No	Continued. Pacemaker capture during each treatment.
7	Transient 2:1 AV block	250	No	1	20	1	4, intermittent	None	None	Recovered	No	Continued.
7	Advanced HB: 3.6 s asystole	250	Yes	2	20	4	Brief	Decreased for other toxicity	Temporary pacemaker	Recovered	No	Received 17 courses, most with only intermittent 2:1.
19	Advanced HB: 3.4 s asystole	250	No	1	23	1	Brief	None	Temporary pacemaker	Recovered	No	Never recurred.
20	Second-degree HB, Mobitz I Wenkebach	170	No	Several	5	1	4 postinfusion	None	None	Recovered spontaneously 3-4 h after infusion was completed	No	Continued. Recurred with each treatment.
Bundle branch block												
4	LBBS [‡]	170/cisplatin	No	6	12	1	Brief	Discontinued	None	Recovered	No	NA
21	LPHB (possible MI) [§]	135/cisplatin	No	5	48	2	Persisted	None	None	Recovered	No	NA

*Previously reported in the literature (3,5).

[†]HB = heart block.[‡]LBBS = left bundle branch block.[§]MI = myocardial infarction.

Table 5. Myocardial infarction and ischemia

Patient no.	Event	Taxol dose, mg/m ² /other chemotherapy	Toxicity grade	History (medications)	Course	Time into infusion	Drug alteration	Resolution reaction	Comments
22	MI	110	5	Hypertension	1	6 h	None	Died	Autopsy: CAD,* massive MI.
23	MI	135/cisplatin	5	Hypertension	1	7 d posttreatment	NA†	Died	Autopsy: Severe CAD with stenosis, fresh thrombus.
24	MI	135	5	NI‡	1	31 h	NA	Died	Autopsy: CAD, cardiomegaly.
25	1. Angina 2. MI	200	4	CAD, angina, CABG,§ angioplasty (Persantine, procardia, nitrates)	3 4	1. During infusion 2. 14 d posttreatment	Interrupted	NI	Angina due to stopping cardiac medications. Taxol resumed at reduced rate.
26	MI	250	4	Hypertension, CAD, CABG, PND, orthopnea (nitrates Nefedipine)	3	14 d posttreatment	Decreased	Recovered	
27	MI	135	4	CAD, MI, aortic bypass, hypertension	1	17 h	Discontinued	Recovered	Protocol violation: Referring MD altered cardiac medications.
21	? silent MI (LPHB)	135	2	Hypertension, diabetes mellitus	5	48 h	None	Recovered	Noted when she presented with dizziness, nausea, headache. Completed course 6. Many concomitant medications.
28	Cardiac ischemia	160	4	(Nitrates)	3	9 h	Discontinued	Recovered	Sudden onset epigastric pain. LDH isoenzymes atypical for MI. ECG anterolateral ST-T abnormalities.
29	Cardiac ischemia	135	4	None	2	12 h	Discontinued	Recovered	Bradycardia with chest pain. Cardiac enzymes WNL. ECG: no changes.
30	Anaphylaxis ECG: Ischemia	250	4	NI	2	5 min	Discontinued	Recovered	ECG changes occurred after intravenous epinephrine for anaphylaxis. No chest pain or cardiac enzyme changes.
31	Chest pain, ECG: Ischemia	135	5	NI	1	7 h	Discontinued	Died	Autopsy: Sepsis due to ovarian cancer, no evidence of MI or CHF. Possible treatment-related death, etiology uncertain.
32	Nonspecific ECG abnormalities	250	3	None	3	8 h	Decreased	NI	

*CAD = coronary artery disease.

†NA = not applicable.

‡NI = no information.

§CABG = coronary artery bypass graft.

||LDH = lactate dehydrogenase.

Table 6. GOG-111: Treatment with cisplatin and Taxol (135 mg/m²) or cyclophosphamide for suboptimal ovarian cancer; cardiac events reported in 8 of 174 patients on the Taxol arm

Patient no.		Grade	Relation	Taxol continued	Comments
*22	MI	5	Unlikely	NA [†]	CAD (autopsy)
23	Orthostatic hypotension	3	Unlikely	Yes	? Autonomic neuropathy
21	LPHB ? MI	2	Possible	Yes	Course 5
33	ECG: Ischemia	2	Unlikely	?	Gastrointestinal obstruction
34	Sinus tachycardia	2	Unlikely	Yes	Scleroderma, cardiac medications, synthroid
36	Sinus tachycardia ST-T changes	2	Unlikely	?	Nausea, vomiting, dehydration probably due to cisplatin
36	First-degree HB	1	Probable	NA	Course 6, completed therapy
37	Hypotension, sinus tachycardia	1	Unlikely	Yes	Hypertension, on antihypertensives

*Reported in literature.

[†]NA = not applicable.

cussed previously in the discussion of myocardial infarction (Table 5). No other life-threatening cardiac events occurred.

Events possibly related to Taxol included LPHB and a questionable myocardial infarction in a diabetic patient after five courses of Taxol. This patient (patient 21) has been described previously and is also included in Tables 4 and 5. Another patient developed asymptomatic first-degree heart block, which was probably due to Taxol, at course 6. One patient developed grade 3 orthostatic hypotension approximately 72 hours after completing her first and second courses of Taxol and cisplatin, and no apparent cause could be identified by the treating physician. This patient may have developed temporary autonomic neuropathy with resolution shortly thereafter, but this diagnosis was not documented. The other events listed in Table 6 appear more likely related to other medical conditions.

At least four patients continued treatment despite the adverse event, and a fifth had completed treatment when first-degree heart block was documented.

Treatment Referral Center Protocol for Refractory Ovarian Cancer: TRC-9103

Preliminary toxicity data have been summarized for the first 696 of more than 1700 refractory ovarian cancer patients registered on the NCI TRC protocol at 39 NCI-designated Comprehensive Cancer Centers (Division of Cancer Treatment NCI, unpublished data). Seven patients had grade 4, seven had grade 3, and seven had grade 2 cardiac toxicity. Grade 1 toxicity was reported in 62 patients (8.9%). The incidence of grade 1 toxicity at each institution varied, suggesting that asymptomatic bradycardia was noted more frequently at some institutions, presumably because of differences in frequency of monitoring of vital signs.

It is important to note that the NCI Common Toxicity

Criteria designate a grade 4 event as any cardiac abnormality that results in cardiac monitoring. Thus, a patient included in this group may not have had a truly life-threatening event but may have undergone cardiac monitoring as a precaution for asymptomatic sinus bradycardia noted on routine determination of vital signs. In two instances, patients were treated in violation of the protocol's requirement for no history of cardiac arrhythmias or congestive heart failure. A beta blocker was discontinued inappropriately to make one of the patients eligible for the clinical protocol. This patient was monitored during therapy and did develop palpitations and NSVT. The clinical indication for beta-blocker therapy was not reported. Two patients underwent cardiac monitoring prophylactically during episodes of sepsis, one in association with hypotension. One patient developed chest pain during Taxol infusion, and an ECG showed ST segment elevation. This patient declined further evaluation or intervention and died soon after. At autopsy, there was no evidence of a cardiac abnormality, and the cause of death, based on a postmortem blood culture, was listed as sepsis. This death, although unexplained, is considered a possible treatment-related death.

If all reported grade 3 and 4 cardiac events are considered, including those non-life-threatening events designated grade 4 only because continuous cardiac monitoring was performed, cardiac toxicity associated with Taxol therapy is 2% (14/696 patients).

Results of Cardiac Monitoring in Five Studies of Taxol Alone or with Cisplatin

Rowinsky et al. previously summarized adverse events in 138 patients who underwent cardiac monitoring during 558 courses of Taxol 15 to 390 mg/m², with or without cisplatin (5). Reed et al. treated 60 patients with Taxol 250 mg/m² and monitored them for a minimum of two cycles. Thirty-one percent of Reed's patients had grade 1

asymptomatic bradycardia. This percentage did not appear to increase with cumulative therapy (Cunnion R, Reed E, personal communication). Two patients had heart block (already described), one had atrial fibrillation (already described), and two had SVT. Overall, then, in 198 patients who underwent monitoring for greater than 678 courses (Table 7), the incidence of NSVT (all asymptomatic) was 2.5%. As previously noted, six of seven patients received cisplatin in combination with Taxol. The incidence of heart block was 2% (only one of four patients had symptoms), of myocardial infarction 0.5%, of atrial fibrillation 0.5%, and of SVT 1%.

DISCUSSION

Taxines are known to affect automaticity and cardiac conduction (6,9,10,12-14). It appears likely that bradycardia and AV conduction abnormalities are caused by Taxol. Similarities in symptoms and cardiac effects among cases of yew poisonings, experimental studies with taxine, and the clinical observations with Taxol cardiotoxicity tend to support this hypothesis.

Asymptomatic bradycardia is the most frequent cardiac event associated with Taxol therapy. It occurs in approximately 30% of patients undergoing continuous cardiac monitoring during 24-hour Taxol infusion. Bradycardia, however, is generally without clinical significance in patients without cardiac risk factors.

Four cases of second- and third-degree heart block have been reported with more than 3400 patients treated (<0.1%). These 4 patients were among the group of 198 monitored patients (incidence of 2% in monitored group). Second- and third-degree heart block is likely underreported because continuous cardiac monitoring is not usually performed. Nevertheless, most documented episodes of second- and third-degree heart block have been asymptomatic and appear to be entirely reversible.

The incidence of VT and VF reported to CTEP is 0.26%. Again, the documented incidence of VT might be higher if more patients were monitored; however, symptoms were rare (2/9 patients) and no deaths were reported.

The incidence of significant atrial arrhythmias (atrial fibrillation, flutter, SVT) reported to CTEP is 0.24%. Many of the reported episodes occurred in patients with a previous history of atrial arrhythmia or with concurrent medical conditions commonly associated with atrial arrhythmias. Although the possibility that Taxol caused or contributed to these arrhythmias cannot be excluded with certainty, it appears more likely that these events were due to other factors.

The incidence of grade 4 and 5 myocardial infarction and cardiac ischemia is also low (0.26% in a database of 3400 patients). This incidence might be expected given the cardiac risk factors noted in these patients (37,38). Although several events were either indirectly related to Taxol (ischemic changes on ECG following epinephrine administered for anaphylaxis) or possibly due to Taxol (development of LPHB and possible silent inferior myocardial infarction in a diabetic, hypertensive patient), most appeared in association with heart disease. The possibility that patients with underlying heart disease developed life-threatening complications because of Taxol treatment cannot be excluded.

To date, there is no evidence of cumulative cardiac toxicity. These data, however, do not rule out the possibility that cumulative toxicity could be demonstrated when more patients are treated for longer periods of time and when the pathophysiology of the rare cardiac events that appear to be related to Taxol are better understood.

With the exception of sinus bradycardia associated with Taxol therapy, cardiac toxicity in patients without cardiac risk factors is uncommon. Most cardiac events have no clinical sequelae. The risk can be compared with other anticancer drugs with cardiac toxicity, including doxorubicin (reported incidence of 0.1% at very low doses to approximately 7% at 550 mg/m²), m-AMSA (reported

Table 7. Summary of adverse events in 198 patients who received Taxol with or without cisplatin while undergoing continuous cardiac monitoring

Institute	Study	No. of patients	Monitored courses	Taxol dose, mg/m ²	Events
JHOC	Phase I*	30	67	15-265	
	Phase I leukemia*	17	28	250-390	
	Phase II ovary*	47	281	110-250	2 HB, sinus bradycardia 29%
	Phase I with cisplatin*	44	182	110-200	5 NSVT, 1 MI
NCI Medicine Branch	Phase II ovary	60	>120	250	2 HB, 2 SVT, 1 A fib; 31% sinus bradycardia (grade I)
Total		198	>678		13 patients, 6.5% (excluding bradycardia)

*Previously reported (5).

incidence of approximately 1% in patients without prior chemotherapy), and even 5-FU (reported incidence of 1.6–18%) (36).

Based on available data, asymptomatic sinus bradycardia is not an indication for discontinuing Taxol therapy or for altering Taxol dose unless the heart rate falls below 35 beats per minute for 2 or more consecutive minutes. Therefore, no specific recommendations for routine monitoring appear indicated. Instead, patients who develop symptoms suggestive of heart block or those who develop severe bradycardia should be evaluated with a 12-lead ECG and should be monitored thereafter. Standard cardiac indications for temporary or permanent pacemaker implantation should be modified only according to the need to continue therapy, the nature and severity of the bradyarrhythmia, its persistence, and the resulting symptoms. For example, patients who develop Mobitz type II block during treatment may be at higher risk for subsequent development of more severe conduction abnormalities and symptoms if treatment is continued.

In GOG-111, which did not require continuous cardiac monitoring, the incidence of cardiac events was higher on the Taxol/cisplatin arm than on the cyclophosphamide/cisplatin arm; however, few serious events occurred, and most could not be ascribed with certainty to Taxol. In GOG-111, NSVT was not reported. Interestingly, all but one case of NSVT reported to CTEP occurred in patients who received Taxol in combination with cisplatin (six patients). Based on all available information including the results from GOG-111, however, even patients receiving Taxol and cisplatin who appear to be at higher risk of NSVT do not require routine cardiac monitoring.

After the initial reports of cardiac events in patients undergoing continuous cardiac monitoring during Taxol infusion, most protocols limited eligibility to patients without possible cardiac risk factors. The treatment recommendations in this report are based on experience with Taxol to date; therefore, they do not apply to patients with possible risk factors who have been excluded from most NCI-sponsored trials. These include patients who would not be expected to tolerate bradycardia (patients with a history of myocardial infarction within 6 months, those with angina, or those with congestive heart failure); those with evidence of altered cardiac conduction (bundle branch block, first-degree AV block); and those on medications known to alter cardiac conduction. These patients might be expected to be at higher risk for development of arrhythmias during Taxol therapy. An Eastern Cooperative Oncology Group trial for patients with potential "risk factors" is expected to define the risk in some patient groups who have generally been excluded from treatment. Because of lack of information, however, such patients will require careful cardiologic evaluation, Holter monitoring pretreatment, and continuous cardiac monitoring during therapy.

The pharmacodynamics of adverse cardiac events caused by Taxol may be difficult to elucidate because severe cardiac toxicity is uncommon. It would be useful, however, to know whether there is a relationship between

adverse cardiac events and Taxol dose, schedule, peak plasma concentration, area under the concentration versus time curve, or other factors. Studies are underway that will attempt to address some of these questions. Additional studies to elucidate the precise mechanism for the alteration in cardiac conduction would be useful. In addition, structure-function studies could help determine the degree of overlap of anticancer activity and cardiac conduction effects in the Taxol molecule.

SUMMARY

Studies with taxines in a variety of animal species, clinical toxicology reports of human yew poisonings, and the structural similarities of taxine B, a known cardiac toxin, and Taxol strongly support the conclusion that Taxol has cardiac effects. In patients without known cardiac risk factors, however, the most common cardiac event is asymptomatic bradycardia. More significant arrhythmias and other adverse events have been documented, but many occurred without symptoms, and not all could be causally linked with certainty to Taxol therapy. The data following treatment of several thousand patients suggest that although adverse cardiac events are associated with Taxol, it can be administered with an acceptable toxicity profile to patients without known cardiac problems. Nevertheless, appropriate evaluation and management are required when patients receiving Taxol develop problems that could be due to cardiac effects. Attention to potential cardiac toxicities by physicians using the drug will provide additional information about Taxol's safety profile.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

²Taxotere is used in this monograph to refer to the drug that now has the generic name docetaxel and the registered trade name Taxotere® (Rhône-Poulenc Rorer Pharmaceuticals Inc., Collegeville, Pa.).

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Overview of Taxol Safety

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The safety profile of Taxol administered intravenously as a single agent has been established based on the experience of 655 patients. Of these patients, 253 were treated in nine phase I studies, and 402 were treated in eight disease-oriented phase II studies. Myelosuppression, specifically neutropenia, was the dose-limiting toxicity in all studies conducted in patients with solid tumors. Neutropenia was schedule dependent and was less severe when Taxol was administered via a 3-hour infusion. Severe hypersensitivity reactions were controlled in the phase II program with a premedication regimen consisting of dexamethasone, an antihistamine, and an H_2 blocker. Cardiovascular toxicities were minimal and do not indicate constant electrocardiographic monitoring during Taxol infusions. Peripheral neuropathy was usually mild to moderate and dose related; however, it rarely caused treatment discontinuation. Additional adverse events associated with Taxol include arthralgia/myalgia, mucositis, nausea and vomiting, and alopecia. [Monogr Natl Cancer Inst 15:131-139, 1993]

PHASE I EXPERIENCE

The nine phase I studies of Taxol¹ are listed in Table 1. With the single exception of a trial at the Johns Hopkins Oncology Center (8), in which patients with acute leukemia were treated, the studies included only patients with solid tumors. In phase I trials, doses ranging from 5 mg/m² per day on a daily times five schedule to 390 mg/m² per day on a single-dose schedule were administered every 3 to 4 weeks. The maximum tolerated dose was defined for a single dose and daily times five schedules using 1- to 24-hour intravenous infusion, with or without premedication for the prevention of hypersensitivity reactions (HSRs). In addition, at the Dana-Farber Cancer Institute, Taxol was administered by continuous intravenous infusion for 5 days with no premedication (9).

In the phase I studies of Taxol, neutropenia was the most frequently reported dose-limiting toxicity (Table 1). Frequency and severity of neutropenia were clearly dose dependent, with either no or mild neutropenia reported for patients who received doses up to 120 mg/m². Severe neutropenia (WHO grade III or IV) occurred in 38% or more of the patients who received Taxol doses of 240 mg/m² or greater per cycle. Because of the various schedules used in the phase I program, severity of neutropenia

was analyzed according to dose without taking into account the length of the infusion.

Initially, continuation of phase I studies was threatened because of severe HSR reported early in the program. At Memorial Sloan-Kettering Cancer Center, where Taxol was administered as a 3-hour intravenous infusion with no premedication, the phase I study was terminated because one patient died of HSR (5). Severe HSRs observed in the early phase I studies led to the investigation of prolonged infusions and to the implementation of a premedication regimen similar to the one used to prevent HSR caused by radiocontrast agents. As shown in Table 2, an increase in infusion duration from 1 or 3 hours to 6 hours or more reduced the frequency of severe HSRs from 12% or more to 5% or less. In addition, no severe HSRs were reported among patients who were premedicated; however, all premedicated patients were given Taxol by prolonged infusion (6 or 24 hours).

Peripheral neuropathy, consisting mainly of neurosensory manifestations, was usually mild to moderate in severity. In two studies, however, neurologic symptoms were the limiting toxicity for Taxol doses of 250 mg/m² or higher, indicating that peripheral neuropathy is dose dependent (10).

Other reported toxicities that seemed to be dose dependent included myalgia/arthralgia, nausea/vomiting, mucositis, and diarrhea. The gastrointestinal toxicities were generally mild or moderate in severity. Mucositis, however, was dose limiting in leukemic patients who received Taxol doses greater than 300 mg/m² (8). Hair loss appeared to be universal and rapid after Taxol treatment; however, many patients in the phase I studies had alopecia before receiving Taxol, which confounded the assessment of the role of Taxol in hair loss.

After the completion of the phase I studies, a wide range of Taxol dosages (135 mg/m² to 250 mg/m²) was proposed. A primary consideration in recommending lower dosages was the extent of prior therapy. The 24-hour intravenous infusion repeated every 3 weeks was, in most cases, the proposed schedule for the disease-oriented studies, because no data were available to confirm whether shorter infusions would be safe when administered with premedication to prevent HSRs (Table 2). The suggested premedication regimen consisted of dexamethasone (20 mg) administered orally at approximately 12 hours and 6 hours before Taxol, an antihistamine (e.g., 50 mg diphenhydramine or its equivalent) administered by intravenous injection 30 to 60 minutes before the start of Taxol infusion, and an H_2 blocker (cimetidine, 300 mg)

*See "Notes" section following "References."

Table 1. Phase I studies

Institution (reference)	Schedule (infusion time)	Highest dose, mg/m ² /d	Premedication	Dose-limiting toxicity
MD Anderson (1)	d × 5 (1 h)	40 × 5	No	Neutropenia
Univ Wisconsin (2)	d × 5 (1–6 h)	40 × 5	Yes	Neutropenia
Johns Hopkins (3)	qd (1–6 h)	265	Yes	Neutropenia
A Einstein (4)	qd (1–24 h)	275	Yes	Neutropenia/PNS [†]
MSKCC (5)	qd (3 h)	230	No	Hypersensitivity
UTSA (6)	qd (6 h)	275	No	Neutropenia/PNS
Mount Sinai (7)	qd (24 h)	300	No	Neutropenia
Johns Hopkins (8)*	qd (24 h)	390	Yes	Mucositis
Dana Farber (9)	q × 5 (120 h)	36 × 5	No	Neutropenia

*Acute leukemia

[†] PNS = Peripheral neuropathy

Table 2. Phase I studies: Severe hypersensitivity reactions

Duration of infusion, h	No. (%) of patients with severe HSR	
	Without premedication*	With premedication
1	6/49 (12)	–
3	3/17 (18)	–
6	1/31 (3)	0/51
24	2/42 (5)	0/43
120	0/20 (0)	–
Total	12/159 (8)	0/94

*3 h versus 24 h without premedication: $P = .138$.

also administered intravenously 30 to 60 minutes before Taxol infusion.

PHASE II EXPERIENCE

The eight phase II studies used to establish the safety profile of Taxol included 349 patients with ovarian cancer and 53 patients with breast cancer (Table 3). Seven completed studies (two of breast cancer and five of ovarian cancer) evaluated the efficacy and toxicity of Taxol in doses ranging from 135 mg/m² to 300 mg/m² given as a 24-hour intravenous infusion every 3 weeks (11–17). In three of these seven studies (15–17), granulocyte-colony stimulating factor (G-CSF) in a dosage of 5 or 10 µg/kg per day was administered as hematopoietic support from day 2 of each Taxol course until satisfactory recovery of leukocyte or neutrophil counts.

The eighth study is a randomized multinational trial being conducted in Europe and Canada under the sponsorship of the National Cancer Institute of Canada (18). This protocol has a bifactorial design and compares two dose levels of Taxol (135 mg/m² versus 175 mg/m²) and two infusion durations (3 hours versus 24 hours) in patients with platinum-pretreated ovarian cancer.

Patient Characteristics

The median age of the 402 patients from phase II studies who were included in the safety database was 55 years

(range 25 to 89 years). Nearly 75% of the patients were fully ambulatory with a performance status of 0 or 1. About 20% of the patients had received prior radiotherapy, and 97% had been previously treated with cytotoxic chemotherapy. About half of the patients had been exposed to more than one chemotherapeutic regimen. Three fourths of the patients had received cisplatin, and 29% had received doxorubicin.

Taxol Dosage and Administration

The dosage of Taxol and the schedule of administration specified in each phase II protocol are detailed in Table 3. In each study, doses of Taxol were adjusted according to the toxicity experienced by the patient during the previous course. Generally, dose reductions of about 20% were recommended if grade III or IV hematologic toxicity occurred or if grade II or III nonhematologic toxicity was persistent. In three studies (15,16,18), grade IV neutropenia or thrombocytopenia that lasted at least 5 to 7 days was the only hematologic indication for reduction of subsequent doses.

In all eight studies, premedication to prevent HSRs was mandatory before each Taxol infusion. As recommended based on the phase I experience, premedication regimens included dexamethasone, an antihistamine such as diphenhydramine, and an H₂ blocker such as cimetidine or ranitidine.

A total of 2117 courses of Taxol were administered in the phase II studies. The median number of courses per patient was five (range 1–34) in the seven completed studies and three (range 1–8) in the interim analysis of the multinational study. Forty-two percent of all Taxol courses were given at a reduced dosage (<90% of initial Taxol dose).

For this safety analysis, the 402 patients were divided into three categories according to their assigned dose in the first course of treatment (Table 4). Each dose group included about one third of the patients. Most of the patients in the low-dose group received a dose of 135 mg/m², and most of those in the intermediate group received 175 mg/m². In the low- and intermediate-dose groups, 28% of the patients (68 of 246) received Taxol as

Table 3. Phase II studies

Study site (reference)	No. of patients	Tumor types	Dose, mg/m ²	Infusion duration, h	G-CSF
GOG (11)	46	Ovarian	170 & 135*	24	-
Johns Hopkins (12)	47	Ovarian	250 & 200 (amended to 170 & 135)	24	-
Albert Einstein (13)	34	Ovarian	250 & 200*	24	-
MD Anderson (14)	25	Breast	250 & 200*	24	-
Multinational (18) [†]	159‡	Ovarian	175 vs. 135 (randomization)	24 vs. 3	-
MCI Medicine Branch (15)	15	Ovarian	170, 200, 250, 300 (escalation)	24	+
NCI Medicine Branch (16)	50	Ovarian	250	24	+
MSKCC (17)	28	Breast	250	24	+

*Lower doses used for high-risk patients.

[†] Interim analysis.

[‡] Two patients never received Taxol and were not evaluated for safety.

Table 4. Phase II studies: Distribution of patients by dose group

Dose group	No. (%) of patients, N = 402
≤150 mg/m ²	113 (28)
3 h	39
24 h	74
151 to 190 mg/m ²	133 (33)
3 h	29
24 h	104
>190 mg/m ²	156 (39)
24 h	66
24 h + G-CSF	90

a 3-hour infusion; all of them were in the multinational study. In the high-dose group, 58% of the patients (90 of 156) received G-CSF.

Myelosuppression

In phase II studies, myelosuppression consisted mostly of neutropenia, which was dose dependent (Table 5) and sometimes led to reduction of subsequent doses of Taxol. Severe neutropenia (WHO grades III and IV) developed in 61% of patients in the low-dose group compared with 82% of the intermediate-dose group and 90% of the high-dose group.

Unexpectedly, neutropenia was also dependent on the schedule. Neutropenia occurred more often and was more severe when the same dose was administered as a 24-hour infusion as opposed to a 3-hour infusion (Table 6). Furthermore, data depicted in Table 6 indicate that the schedule of administration has more effect on severity of neutropenia than does the dose level.

Analysis of the impact of G-CSF treatment on the duration and severity of Taxol-induced neutropenia was restricted to studies that included hematopoietic support (15-17). This analysis was further restricted to the 90

patients in the 24-hour high-dose arm who had at least two complete blood cell counts between day 2 and day 17 of treatment. Of these 90 patients, 60 received G-CSF and 30 did not. Severe neutropenia was common in both groups (Table 7). However, 16 (53%) of the 30 patients without hematopoietic support had two consecutive neutrophil counts of less than 500 cells/mm³ and, for three of these 16 patients, the duration of severe neutropenia was more than 1 week. In contrast, only 17 (28%) of the 60 patients who received G-CSF had two consecutive neutrophil counts of less than 500 cells/mm³, and in no case did the severe neutropenia last more than 7 days. Thus, G-CSF does not seem to affect the severity of Taxol-induced neutropenia but can shorten its duration.

Although Taxol-induced neutropenia occurred frequently and was severe in all eight phase II studies, it was relatively well tolerated. Only 13% of the 2117 administered courses were associated with an infectious episode. Most of these episodes were localized (such as to the urinary or upper respiratory tract), and some were disease related. Twenty-six cases of septicemia (affecting 6% of the 402 patients) were reported in the medical records, but for some cases no confirmatory blood cultures were available. Seven infectious episodes led to death. Five of them were associated with severe neutropenia attributable to Taxol administration.

Compared with neutropenia, severe thrombocytopenia occurred infrequently. Thirty-nine (10%) of the 402 patients had a nadir platelet count below 50 000 platelets/mm³ at least once during treatment. Thrombocytopenia was dose dependent (Table 5) but never dose limiting. Seventy-eight patients (19%) had bleeding episodes, but most of these hemorrhages were localized and appeared to be related to the disease rather than to therapy. Fourteen patients (3%) required platelet transfusions.

Anemia (hemoglobin <11 g/dL) was observed in 90% of the 402 patients and also appeared to be dose dependent (Table 5). In contrast to neutropenia and thrombocytopenia, incidence and severity of anemia seemed to in-

Table 5. Phase II studies: Worst myelosuppression by dose

Hematologic toxicity/dose group	Percent of patients by WHO grade			Median nadir counts
	0	I/II	III/IV	
Neutropenia				
All Patients	8	13	79	$0.2 \times 10^3/\text{mm}^3$
By Dose				
$\leq 150 \text{ mg/m}^2$ (N = 113)	10	29	61	$0.6 \times 10^3/\text{mm}^3$
151 to 190 mg/m^2 (N = 132)	9	9	82	$0.2 \times 10^3/\text{mm}^3$
$> 190 \text{ mg/m}^2$ (N = 156)	6	4	90	$0.1 \times 10^3/\text{mm}^3$
Thrombocytopenia				
All Patients	73	17	10	$152 \times 10^3/\text{mm}^3$
By Dose				
$\leq 150 \text{ mg/m}^2$ (N = 113)	87	10	4	$197 \times 10^3/\text{mm}^3$
151 to 190 mg/m^2 (N = 133)	86	10	5	$165 \times 10^3/\text{mm}^3$
$> 190 \text{ mg/m}^2$ (N = 156)	53	29	19	$111 \times 10^3/\text{mm}^3$
Anemia				
All Patients	10	66	24	9.1 g/dL
By Dose				
$\leq 150 \text{ mg/m}^2$ (N = 113)	12	69	19	9.4 g/dL
151 to 190 mg/m^2 (N = 133)	14	74	11	9.7 g/dL
$> 190 \text{ mg/m}^2$ (N = 156)	4	56	39	8.3 g/dL

Table 6. Phase II studies: Worst neutropenia by schedule*

Dose group/infusion time	Percent of patients by WHO grade			Median nadir counts
	0	I/II	III/IV	
$\geq 150 \text{ mg/m}^2$				
3 h (N = 39)	26	59	15	$1.51 \times 10^3/\text{mm}^3$
24 h (N = 74)	1	14	85	$0.3 \times 10^3/\text{mm}^3$
151 to 190 mg/m^2				
3 h (N = 29)	24	21	55	$0.87 \times 10^3/\text{mm}^3$
24 h (N = 103)	5	6	89	$0.19 \times 10^3/\text{mm}^3$

*Dose/schedule interaction: $P = .04$. All patients treated at a dose of $\leq 150 \text{ mg/m}^2$ versus 151 to 190 mg/m^2 : $P = .001$. All patients treated via 3 h versus 24 h: $P = .0001$.

Table 7. Phase II studies: Duration of neutropenia by G-CSF treatment

Duration of neutropenia†	No. (%) of patients*	
	No G-CSF (N = 30)	With G-CSF (N = 60)
With no ANC < 500	3 (10)	11 (18)
With 1 ANC < 500	11 (37)	32 (53)
With 2 ANC < 500	16 (53)	17 (28)
< 7 days	13	17
≥ 7 days	3	0

*Analysis restricted to patients treated with doses greater than 190 mg/m^2 and for whom two complete blood cell counts between day 2 and 17 are available.

† ANC = absolute neutrophil count.

crease with increasing exposure to Taxol. The median nadir hemoglobin value was 10 g/dL (range 5.8–14.7

g/dL) for the first course of treatment versus 9.1 g/dL (range 8.2–14.7 g/dL) for the course with the lowest nadir. Severe anemia (hemoglobin < 8 g/dL) occurred in 24% of the patients overall and occurred more often in patients with anemia at study entry (40%) than in those with normal baseline hemoglobin levels (13%). Thirty-four percent of all patients, but only 18% of those with normal baseline hemoglobin levels, received packed cell transfusions.

Hypersensitivity Reactions

Phase II experience demonstrates that the problem of severe HSRs, which hampered the early development of Taxol, has been resolved. In fact, among the 402 patients treated in the phase II studies, who before each Taxol infusion received premedication to prevent HSRs, 10 (2%) patients had severe HSRs that required symptomatic treatment, infusion discontinuation, or both (Table 8). Of

Table 8. Phase II studies: Hypersensitivity reactions

Severity/symptoms	No. (%) of patients (N = 402)	No. (%) of courses (N = 2117)
Severe*	10 (2)	10 (<1)
Minor	156 (39)	396 (19)
More frequent symptoms:		
Flushing	129 (32)	312 (15)
Rash	37 (9)	55 (3)
Hypotension	14 (3)	20 (1)
Dyspnea	17 (4)	15 (1)
Tachycardia	12 (3)	15 (1)

*Severe HSR: requiring treatment and/or infusion discontinuation.

note, all these severe HSRs were transient with rapid recovery. They occurred in either the first or second course of treatment and generally within the first hour, often the first minutes, of the Taxol infusion. Of the 10 patients with severe HSRs, nine had the infusion discontinued and seven received symptomatic treatment such as bronchodilators, epinephrine, antihistamines, or corticosteroids. Six of the 10 patients continued Taxol therapy with no subsequent severe HSRs. All rechallenge infusions were conducted with either additional doses of the premedication regimen, a decreased rate of infusion, or both.

Minor HSRs were frequent (Table 8). They consisted almost exclusively of flushing or rashes and never required symptomatic treatment. Minor HSRs occurred throughout the treatment period, and their severity did not increase with repeated administration of Taxol.

Important information regarding the relationship between risk of HSRs and duration of infusion among premedicated patients was provided by the interim analysis of the multinational study (18). In this study, patients received Taxol by either a 3-hour or a 24-hour infusion. For both infusion times, the frequency of severe and minor HSRs was comparable (Table 9). These interim results were supported by later analysis of this study and by analysis of other ongoing studies using a 3-hour infusion in more than 500 patients (Bristol-Myers Squibb, data on file).

Cardiovascular Toxicity

The occurrence of HSRs in the early clinical trials of Taxol motivated investigators to observe patients carefully during Taxol administration. This intense monitoring generated detailed information on cardiac function during therapy. None of the phase II studies included a non-Taxol control arm, however. Such a control group would have enabled a differentiation between cardiac events that were induced by Taxol and those possibly related to the underlying malignancy or to prior cytotoxic therapy.

The most frequent cardiovascular events reported during Taxol administration in phase II studies were declines in heart rate and in blood pressure (Table 10). To detect

Table 9. Hypersensitivity reactions by schedule

Duration of infusion/ severity of HSR	No. (%) of patients
3 h (N = 68)	
severe HSR	1 (1)
minor HSR	22 (32)
24 h (N = 89)	
severe HSR	1 (1)
minor HSR	33 (37)

Table 10. Phase II studies: Hypotension and bradycardia during Taxol infusion*

Changes in vital signs	No. (%) of patients	No. (%) of courses
Heart rate <50 beats per minute	35/378 (9)	64/1796 (4)
Systolic drop in blood pressure \geq 30 mm Hg	82/387 (22)	118/1581 (7)
Both in the same course	5/373 (1)	6/1532 (<1)

*Day 1 or 2 of each course.

immediate effects of Taxol infusion on blood pressure or heart rate, the analysis was restricted to events occurring on day 1 or day 2 of each course. Thirty-five (9%) of the 402 patients experienced bradycardia (heart rate less than 50 beats per minute) on the day of or the day after Taxol infusion. The incidence of bradycardia is most likely related to the frequency and type of cardiac monitoring performed on these patients. For example, incidence of bradycardia varied from 0 to 38% of patients in the phase II studies.

Eighty-two (22%) patients had a drop in systolic blood pressure of 30 mm Hg or more relative to the baseline pressure reading. Only five (1%) patients had bradycardia and hypotension recorded in the same course. With the exception of the six cases described below, changes in vital signs were asymptomatic and were identified by routine monitoring.

Six of the 402 patients experienced significant cardiovascular events for which a relationship to Taxol could not be ruled out. Three of these events were discovered during continuous electrocardiographic monitoring: one patient had an isolated and asymptomatic ventricular tachycardia, and two patients had atrioventricular blocks (associated with asystole in one case) that resolved spontaneously but justified the placement of a pacemaker to avoid recurrence during subsequent Taxol treatment. In addition, on initiation of electrocardiographic monitoring, one patient had tachycardia and palpitations that improved after administration of albuterol and a corticosteroid; this event was retrospectively considered an HSR. Finally, two patients had syncopal episodes after discontinuation of Taxol.

Neurologic Toxicity

Peripheral neuropathy was observed in 62% of the 402 patients treated in the phase II studies. Neurosensory

manifestations were predominant and included numbness, tingling, and burning pains generally in the extremities. Neurologic examination, when performed, often revealed a loss of sensation in the extremities and less frequently a decrease of deep tendon reflexes.

Incidence and severity of neurologic symptoms were clearly dose dependent (Table 11). About 45% of patients receiving doses of 190 mg/m² or less were affected compared with more than 80% of those receiving higher doses. Neurologic symptoms were generally mild or moderate in severity, but 1% of patients receiving doses of 190 mg/m² or less experienced severe symptoms compared with 10% of those receiving higher doses.

Neurologic symptoms occurred early in the treatment period (44% of patients had neurologic symptoms during the first course) and increased in frequency and severity with increased exposure to Taxol. Severe neurologic symptoms usually improved after dose reduction and caused discontinuation of Taxol for less than 2% of the patients. Neurologic toxicity was usually reversible after termination of Taxol therapy.

Arthralgia/Myalgia

Arthralgia and myalgia were often reported, especially at high dose levels. They were usually transient, occurring 2 or 3 days after Taxol administration and resolving within a few days. Patients usually complained of pain in the large joints. Of the patients treated at doses of 190 mg/m² or less 43% complained of musculoskeletal symptoms compared with three fourths of those treated at higher doses (Table 11). Arthralgia and myalgia mostly remained mild or moderate in severity. Among the patients treated at doses greater than 190 mg/m², G-CSF contributed to musculoskeletal symptoms. The incidence of arthralgia or myalgia increased from 61% of patients who did not receive G-CSF to 86% of those who did.

Alopecia

Alopecia affected almost all patients in phase II studies, even at low doses of Taxol. Information in the database

was insufficient to characterize the intensity, the dose dependency, and the time to occurrence of Taxol-induced alopecia. However, when its severity was reported, alopecia was usually generalized. In the multicenter study (18) in which alopecia was prospectively recorded, 66% of patients without baseline alopecia displayed severe hair loss during Taxol therapy.

Digestive and Hepatic Toxicity

Digestive toxicity was limited. Approximately half of the 402 patients experienced emesis or diarrhea, but these events were rarely severe (<5%). Requirement for antiemetic medication was minimal; however, all patients did receive dexamethasone as part of their premedication regimen.

Mucositis was experienced by 39% of the patients and was dose dependent. The incidence was 60% among patients receiving doses greater than 190 mg/m² as opposed to 26% among those receiving lower doses. Mucositis was usually moderate in severity and was never dose limiting.

Approximately one third of the 402 patients had abnormal liver function at baseline. Consequently, evaluation of changes in liver function caused by Taxol was confounded by changes in hepatic function caused by underlying disease. To accurately assess changes in liver function resulting from Taxol therapy, an analysis was performed that included only patients with normal liver function at baseline (Table 12). Results indicated a dose-dependent effect for Taxol; however, even in these patients with widely disseminated malignancies, the changes in liver function were minimal at Taxol doses of 190 mg/m² or less.

To further analyze the effect of Taxol on liver function, the safety profile of Taxol for patients with abnormal liver function at baseline was compared with the safety profile for patients with normal liver functions at baseline (Table 13). For this analysis, abnormality was defined as a liver function value greater than 1.25 times the upper limit of normal (WHO grade I or greater). Except for nausea, vomiting, and diarrhea, the frequency of each adverse event ascribed to Taxol was comparable between the two groups of patients. Additional studies are necessary to assess the safety of Taxol therapy in patients who have more severe hepatic impairment. Data currently available are, however, not sufficient to support the use of Taxol in patients with more severe liver enzyme or bilirubin alterations.

DISCUSSION

The safety profile of single-agent Taxol was similar for each of the eight phase II studies and was consistent with the phase I experience. A number of adverse events frequently associated with anticancer chemotherapy were encountered during Taxol treatment; these included myelosuppression, peripheral neuropathy, alopecia, and changes in gastrointestinal and liver function. Events less commonly seen with anticancer chemotherapy that were

Table 11. Phase II studies: Worst peripheral neuropathy and arthralgia/myalgia by dose

Dose group/severity	Percent of patients	
	Peripheral neuropathy	Arthralgia/myalgia
≤ 150 mg/m ² (N = 113)		
WHO grade I/II	39	41
WHO grade III	-	1
151 to 190 mg/m ² (N = 133)		
WHO grade I/II	41	32
WHO grade III	2	4
> 190 mg/m ² (N = 156)		
WHO grade I/II	73	58
WHO grade III	10	7

Table 12. Phase II studies: Changes in liver function tests*

Liver function test/severity	Percent of patients		
	$\leq 150 \text{ mg/m}^2$	151 to 190 mg/m^2	$> 190 \text{ mg/m}^2$
Bilirubin			
WHO grade I/II	5	3	12
WHO grade III/IV	—	—	4
Alkaline phosphatase			
WHO grade I/II	14	15	34
WHO grade III/IV	—	1	3
SGOT†			
WHO grade I/II	7	11	26
WHO grade III/IV	—	—	2

*Analysis restricted to patients with normal baseline.

† Serum glutamic oxaloacetic transaminase.

Table 13. Phase II studies: Frequency of Taxol-induced adverse events, by baseline liver function

Toxicity	Percent of patients	
	Normal liver function, N = 295	Abnormal liver function,* N = 90
Myelotoxicity		
Neutropenia, WHO grade III/IV	80	73
Thrombocytopenia, WHO grade III/IV	7	12
Anemia, WHO grade III/IV	22	28
Any HSR	40	44
Cardiovascular		
Hypotension	26	21
Bradycardia	12	13
Other		
Peripheral neuropathy	62	57
Arthralgia/myalgia	54	58
Alopecia	82	82
Emesis	56	67
Diarrhea	41	49
Mucositis	38	41

*Abnormal liver function: a value on liver function testing more than 1.25 times the upper normal limit.

reported to be associated with Taxol administration included hypersensitivity reactions, bradycardia, and drop in blood pressure during infusion.

Although neutropenia was the principal dose-limiting toxicity reported for Taxol, it was usually of short duration and was infrequently associated with infectious episodes. At doses of 190 mg/m^2 and below, hematopoietic support with colony-stimulating factors generally was not necessary. The severity of Taxol-induced neutropenia was unique in that it was dependent on the schedule of administration; neutropenia was significantly less severe when similar doses were given as a 3-hour infusion rather than as a 24-hour infusion.

In contrast with neutropenia, severe thrombocytopenia was rare, and platelet transfusions were almost never required during therapy. Mild anemia occurred frequently and was cumulative with repeated administration of Taxol. Such hematologic toxicity justifies frequent moni-

toring of blood counts during Taxol therapy to detect related complications. In cases of prolonged myelosuppression (neutropenia $< 500 \text{ cells/mm}^3$ for 5 to 7 days), dose reduction is indicated. Dose reductions based on duration of cytopenia rather than severity (nadir count) seem to be justified by the short duration of Taxol-induced neutropenia. In addition, any patient displaying febrile neutropenia requiring intravenous antibiotics should be treated at a reduced dose.

Peripheral neuropathy and arthralgia/myalgia were also dose dependent, but unlike myelotoxicity, severe symptoms were unusual at Taxol doses of 190 mg/m^2 or less. Neurologic toxicity did not appear to be dependent on the schedule of administration. When severe neurologic or musculoskeletal toxicity occurred, dose reductions seemed to be effective in controlling it; further treatment at reduced Taxol doses was tolerated. When G-CSF was used simultaneously with Taxol, bone pain and arthralgia were

more frequent and in part related to G-CSF treatment.

Gastrointestinal toxicities and changes in liver function were likewise dose dependent but remained mild or moderate in severity at doses up to 190 mg/m². Alopecia occurred frequently and was severe.

In addition to these dose-dependent adverse events, HSRs were reported, but they did not compromise safety. When adequate premedication was administered, severe HSRs were rare during both 24-hour and 3-hour infusions. Nevertheless, even with premedication, vital signs should be monitored carefully during the first hour of Taxol administration, especially during the first or the second course of treatment. The occurrence of any severe HSRs justifies immediate discontinuation of the Taxol infusion and may require treatment of symptoms. Continuation of Taxol therapy for patients who experience severe HSRs is possible if adequate premedication is given and a slower infusion rate is used at least during the first hour of Taxol administration (19). Minor HSRs, mainly flushing and rashes, occurred frequently and were recurrent but did not become more severe during later courses of therapy. Such reactions should not prevent completion of Taxol therapy.

Bradycardia and drop in blood pressure during Taxol infusion were the only frequently documented cardiac events; these changes in vital signs were generally asymptomatic. The information gathered in the phase II database as well as in several other ongoing studies in the United States and in Europe indicates that routine electrocardiographic monitoring is not required during Taxol treatment. Most of the data generated to date, however, have been limited to patients with no known active cardiac disorder.

In summary, at doses up to 190 mg/m² administered as a 24-hour infusion, the clinical tolerance of Taxol is acceptable and Taxol-induced toxicity is easily manageable. Use of shorter infusions (i.e., 3-hour infusions) needs to be further investigated to confirm comparable efficacy with longer infusions, but shorter infusions may represent a convenient and safe schedule for Taxol administration. Prospective studies are ongoing to determine whether the use of higher doses of Taxol are justified by a dose-response relationship. Until results of such trials are available, doses of 135 mg/m² to 190 mg/m², depending on the extent of prior therapy, can be safely administered to patients with solid tumors.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Taxol: A History of Pharmaceutical Development and Current Pharmaceutical Concerns

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Taxol, a unique diterpene anticancer compound derived from the bark of the *Taxus brevifolia* (Pacific yew) tree, induces cytotoxicity by a novel mechanism of action. An antimicrotubule agent, Taxol promotes the formation and stabilization of the tubulin polymer unlike other anticancer agents that induce microtubule disassembly. Because of its poor aqueous solubility, Taxol is formulated as a solution in 50% Cremophor EL and 50% dehydrated alcohol, USP. The Cremophor EL and dehydrated alcohol vehicle used in the formulation of Taxol creates some interesting challenges for its preparation and administration. The pharmaceutical concerns associated with the preparation and administration of Taxol are discussed. [Monogr Natl Cancer Inst 15:141-147, 1993]

Taxol¹ is a unique diterpene anticancer compound derived from the bark of the *Taxus brevifolia* (Pacific yew) tree. A crude extract of the bark demonstrated antineoplastic activity in preclinical tumor screening 30 years ago as part of the National Cancer Institute's (NCI's) large-scale screening program (1). Wani et al. isolated and described Taxol, the active component of the extract, in 1971 (1). In 1979, Schiff and coworkers rekindled interest in the development of Taxol by demonstrating its novel mechanism of action (2,3). Taxol stabilizes the tubulin polymer and promotes microtubule assembly, rather than inducing microtubule disassembly like the antimicrotubule agents colchicine, vincristine, and vinblastine. This stabilization results in the inhibition of the normal dynamic reorganization of the microtubule network. Clinical trials of Taxol began in 1983. The results of the early clinical trials spurred considerable interest in continued development. To date, encouraging response rates (complete and partial) have been reported in single-agent phase II studies in breast cancer (56%) (4), previously untreated non-small-cell lung cancer (21% and 24%) (5,6), head and neck cancer (41%) (7), and refractory ovarian cancer (21%, 30%, and 36%) (8-10). Taxol in combination with granulocyte-colony stimulating factor (G-CSF) is also being studied, but it is not yet known if higher doses with G-CSF are more effective than lower doses without G-CSF support (11,12). Preliminary results in prostate cancer, colon cancer, renal cancer, cervical cancer, and melanoma are poor; however, some of these early studies may have used suboptimal doses. In December 1992, after nearly 30 years of research and development, the FDA

approved Taxol for the treatment of metastatic ovarian cancer after failure of first-line or subsequent chemotherapy. Because Taxol is becoming more widely available, this paper will describe the unique pharmaceutical issues related to Taxol preparation and administration.

PHARMACEUTICAL DEVELOPMENT

After Taxol's initial promising results against murine tumors, drug formulation development work was begun. Because the drug was not active when administered orally, efforts were directed toward a formulation suitable for intravenous administration. Taxol is poorly soluble in water (less than 0.01 mg/mL) and other common vehicles used for the parenteral administration of drugs. General approaches used to formulate drugs for intravenous administration are presented in Table 1. All of these approaches, with the exception of pH adjustment/salt formation, were evaluated for the solubilization of Taxol. Taxol does not contain groups that may be ionized in an acceptable pH range (Fig. 1) to allow salt formation.

The solubilities of Taxol in various aqueous vehicles and organic solvents are presented in Table 2. Most of these data were determined after mixing the drug with solvent for 1 to 2 hours. They represent approximate rather than equilibrium solubilities (A. J. Repta, unpublished observation, 1978). Taxol is substantially soluble in several organic solvents. However, when a water-miscible organic solvent containing Taxol at near its saturation solubility is diluted with water, the drug precipitates. The solubility of a water-insoluble solute over a given concentration range often increases exponentially with the fraction of cosolvent added. Therefore, dilution with water of an organic solvent saturated with a poorly water-soluble drug, such as Taxol, usually results in precipitation of the drug. Fig. 2 shows the exponential increases in approximate Taxol solubility as a function of increasing polyethylene glycol 400 (PEG 400) concentration (A. J. Repta, unpublished observation, 1978).

Solutions of Taxol in PEG 400 were evaluated as a potential formulation approach. A 75% solution of PEG 400 in water containing 16 mg/mL of Taxol was found to be chemically stable by high-performance liquid chromatographic (HPLC) analysis and free of visible particulates for up to 14 days at 25 °C. However, precipitation or cloudiness was noted when Taxol solutions (16 to 25 mg/mL) were added through the Y-site port of an intra-

*See "Notes" section following "References."

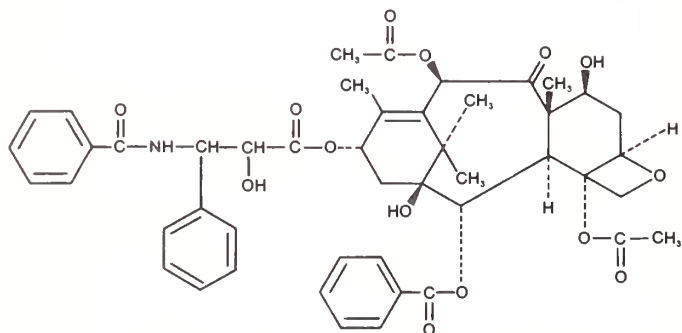
Table 1. Approaches to increase drug solubility

Approach	Examples
pH adjustment/salt formation	Hydrochloride, citrate, lactate, meglumine, sodium, potassium
Cosolvent	Ethanol, dimethylsulfoxide, polyethylene glycols, propylene glycol
Complexation	Cyclodextrins, povidone
Oil-water emulsions	10%-20% Soybean oil
Micellar solubilization	Cremophor EL, polysorbate 80
Synthesis of prodrugs	See (33,34)

venous administration set containing infusion fluid (A. J. Repta, unpublished observation, 1978). Yalkowsky used an instrumental method (13) to study the precipitation of Taxol from 70% dimethylsulfoxide (DMSO)/30% PEG 400 after addition to infusion fluids (S. H. Yalkowsky, unpublished observation, 1985). Precipitation of Taxol in infusion fluids could be minimized or eliminated by carefully adjusting the rate of addition of the drug-containing vehicle to the moving infusion fluid in the intravenous administration set or by decreasing the concentration of Taxol in the vehicle. This method of Taxol administration presents many opportunities for errors and adverse events. These include erratic and subtherapeutic dosing due to drug precipitation and retention by in-line filters. Additionally, in preclinical efficacy testing in mice, Taxol administered intraperitoneally (IP) in aqueous PEG 400 was less active against IP-implanted B16 melanoma than Taxol administered IP either as an aqueous suspension or as a solution containing the nonionic surfactant Cremophor EL® (a polyoxyethylated castor oil).

The solubility of Taxol in soybean oil (Table 2) is quite low, precluding the incorporation of significant concentrations of Taxol into simple oil-water emulsions.

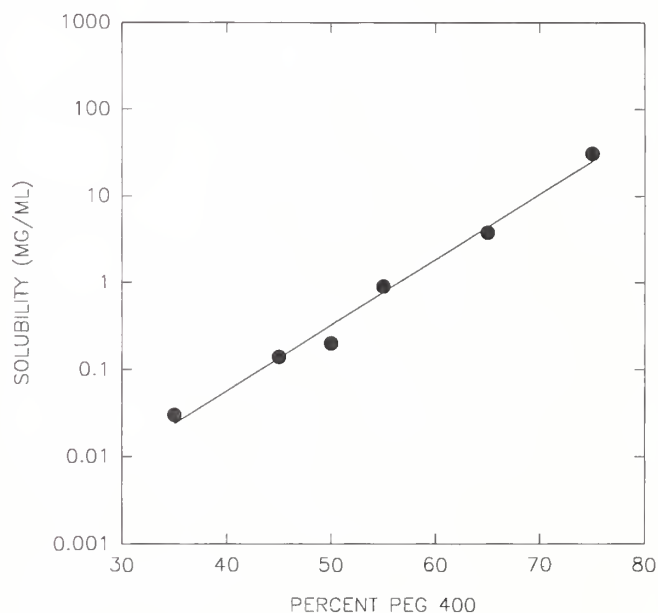
Solubilization of compounds with surfactants allows for dilution of saturated or near-saturated solutions. Generally, above the critical micelle concentration, a linear relationship exists between solubility of a solute and the fraction of surfactant added. Therefore, dilution of a Taxol solution in Cremophor EL with aqueous diluents should yield solutions for a broad range of dilutions. However, the equilibrium solubility of Taxol in 5% Cremophor EL/

**Fig. 1.** Chemical structure of Taxol.**Table 2.** Approximate solubility of Taxol in various solvents at 25 °C

Solvent	Solubility, mg/mL
Methylene chloride	≥ 19
Acetonitrile	≥ 22
n-Heptane	< < 1
Ethanol	~ 39
Isopropanol	~ 12
75% Isopropanol/water	~ 0.2
75% Propylene glycol	< 1.4
30% Polyvinylpyrrolidone in water	≤ 0.3
75% PEG 400*	31
65% PEG 400	3.8
55% PEG 400	0.9
50% PEG 400	0.2
45% PEG 400	0.14
35% PEG 400	0.03
Soybean oil	0.3
Triacetin	75

*Polyethylene glycol 400

5% dehydrated alcohol 0.9% sodium chloride injection (NS) is only about 0.1 mg/mL (A. J. Repta, unpublished observation, 1978). Supersaturated solutions may be prepared at concentrations of 0.6 mg/mL or greater in

**Fig. 2.** Relationship between the solubility of Taxol and the percentage of PEG 400 contained in mixed solvents (A. J. Repta, unpublished observation, 1978).

this vehicle by the dilution of a 6-mg/mL solution of Taxol in 50% Cremophor EL/50% dehydrated alcohol, USP. Unfortunately, it is not always possible to predict when the drug may precipitate from such solutions. Several studies were initiated to evaluate the chemical and physical stability of solutions of Taxol in 50% Cremophor EL/50% dehydrated alcohol, USP, diluted in either NS or 5% dextrose injection, USP (D5W) to final Taxol concentrations of 0.6 mg/mL or less (R. E. McIntyre, D. L. Francis, unpublished results, 1983; P. Lim, unpublished results, 1983). Solutions were examined visually for evidence of particulate formation. In most cases, small amounts of particulates, usually a few fiber-like or irregularly shaped white particles, were observed at most intervals up to 24 hours. The quantity of particles appeared to be greater in the solutions with a higher Taxol concentration (0.6 mg/mL) and seemed in some cases to increase somewhat over time. HPLC analysis of the filtered solutions, however, demonstrated that minimal Taxol was lost to decomposition or precipitation over periods as long as 24 hours. Solutions were found to contain 96% or more of their initial concentration after 24 hours. Although these data provide some assurance that most of the drug remains intact and in solution over 24 hours, the possibility of drug precipitation from a supersaturated solution must not be discounted.

At this point in the history of the development of Taxol (about 1980), the formulation approach using 50% Cremophor EL/50% dehydrated alcohol, USP, diluted in NS or D5W to a final concentration of 5% Cremophor EL/5% dehydrated alcohol or less, represented the most viable option for the intravenous administration of drug to humans in initial clinical trials. Preclinical toxicology was performed using Taxol in a Cremophor EL diluent, and additional formulation studies were conducted to support the clinical use of this vehicle.

Other Formulation Studies

Although Taxol has been studied clinically since 1983, NCI contractors have continued to attempt to develop a safe and more convenient way to deliver Taxol parenterally. Potential prodrugs have been prepared and evaluated by Mathew and his coworkers and by Deutsch and colleagues (14,15). Tarr et al. described a Taxol-containing emulsion that employs triacetin to increase the incorporation of the drug into the oil phase of the emulsion (16). All of these approaches require substantial additional preclinical evaluation for activity pharmacokinetic profile, and toxicity before their clinical usefulness can be assessed.

Chemical and Physical Stability of Diluted Solutions

The chemical stability of dilute Taxol solutions (0.3 to 1.2 mg/mL) in NS or D5W is acceptable, with little or no decomposition observed over 24 hours at room temperature. However, as described earlier, solutions examined visually for evidence of particulate formation frequently showed small amounts of fiber-like or irregularly shaped

white particles (within acceptable limits established by the USP Particulate Matter Test for Large Volume Parenterals) during a 24-hour observation period. Since more particles were observed in the 0.6 mg/mL solution, a cautious 3-hour stability limit (e.g., the time from initial preparation to the end of the infusion) was recommended for initial clinical trials. After a few years of clinical experience using these supersaturated solutions, no reports of significant precipitation or other observations consistent with loss of the drug by precipitation were forthcoming. After an additional study to confirm the chemical stability and lack of significant loss of drug to precipitation, the stability limit of the 0.6 mg/mL solution was extended to 12 hours and later to 24 hours in 1990 (17). The observation of particles in the diluted solutions of Taxol prompted the recommendation that the solution be filtered through an in-line filter. Supplemental studies performed by Bristol-Myers Squibb (BMS) demonstrated that Taxol solutions diluted to 0.6 mg/mL and 1.2 mg/mL in 5% dextrose and 0.9% sodium chloride injection, USP (D5NS), or 5% dextrose in Ringers injection (D5W-R) are stable for up to 27 hours at room temperature (S. Evans, unpublished observation, 1992).

The Clinical Dosage Form

Taxol for injection concentrate is currently available in 30-mg (5-mL) single-dose vials. Each milliliter of solution contains 6 mg Taxol, 527 mg of Cremophor EL, and 49.7% (vol/vol) dehydrated alcohol. This concentrated solution must be further diluted with NS, D5W, D5NS, or D5W-R prior to administration. Although shelf-life studies are ongoing, generally the intact vials are stable for up to 5 years at 4 °C. The commercial product is stable until the date indicated on the package when stored under refrigeration, 2 °C to 8 °C (36 °F to 46 °F), in the original container.

ISSUES REGARDING TAXOL PREPARATION AND ADMINISTRATION

The Cremophor EL and dehydrated alcohol vehicle used in the Taxol formulation creates some interesting challenges for the preparation and administration of Taxol solutions. Knowledge of proper solution containers, intravenous tubing sets, in-line filters, and intravenous catheters required for safe Taxol administration is essential.

Plasticizer Extraction

Polyvinylchloride (PVC) infusion bags and intravenous administration sets usually contain diethylhexylphthalate (DEHP) as a plasticizer to maximize component flexibility. DEHP leaches to some extent into aqueous infusion fluids and blood products that come in contact with PVC materials (18,19). Cosolvents and surfactants may increase the amount of plasticizer leached. There is some debate about the dangers associated with clinical exposure to

phthalate plasticizers (20,21). A study in rats showed no measurable acute toxicity associated with exposure to levels of DEHP expected from the transfusion of 12 units of blood stored for 21 days in PVC bags. However, exposure of animals to chronic high doses (more than 100 mg/kg) has resulted in toxic effects including growth retardation, liver weight increase, liver damage, testicular atrophy, teratogenicity, and carcinogenicity (22). On the basis of available information, it seems reasonable to limit patient exposure to DEHP as much as possible. Waugh and colleagues evaluated the quantities of DEHP extracted from PVC infusion devices by the Taxol formulation (17). Substantial quantities of DEHP were extracted by all formulation concentrations tested. On the basis of these data, it is recommended that DEHP-plasticized PVC infusion bags and administration sets not be used.

Materials for Preparation and Administration

Taxol can be prepared in glass bottles, polyolefin containers, or any other fluid container that does not contain plasticizers within the fluid pathway surfaces. Examples of suitable products include the McGaw Excel® bag made with a polyethylene-polypropylene copolymer external layer and a polypropylene internal fluid contact surface or the McGaw Accumed® bottle made of rigid polypropylene. Also, some of the flexible bags designed for use with fat emulsion or "3-in-1" total parenteral nutrition administration are made from ethylene vinyl acetate (EVA), which does not contain phthalate plasticizers and would be considered acceptable. Examples of these products include the EVA® bag (Keller Medical, San Diego, Calif.) or the Travamulsion® bag (Baxter, Deerfield, Ill.). However, some products marketed as "non-DEHP" vinyl material contain other plasticizers [e.g., Tris (2-ethylhexyl) trimellitate]. Until the leaching characteristics of these plasticizers and the possible clinical consequences are determined, it is recommended that nonplasticized solution containers be used for Taxol preparation.

Likewise, Taxol should not be infused through intravenous administration sets with DEHP-plasticized fluid pathways. Most tubing sets recommended for use with nitroglycerin or fat emulsion infusions are suitable for use with Taxol infusions. However, care must be exercised to ensure selection of an intravenous administration set that incorporates a DEHP plasticizer-free fluid pathway. Tubing manufacturers usually accomplish this by lining the administration set with a polyolefin material, usually polyethylene or polypropylene, to create a nonplasticized fluid inner contact surface. Careful attention should be paid to the tubing segment that contacts the pumping mechanism. The majority of acceptable administration sets incorporate a silicone (Silastic) segment; however, some administration sets labeled for use with fat emulsions incorporate a DEHP-plasticized PVC section that attaches to the pumping mechanism. These sets are not recommended for Taxol administration. As with solution containers, PVC tubing made flexible with other plasticizers should not be used until specific compatibility with the Taxol formulation is demonstrated. Questions about drip chamber and

bag spike composition frequently arise. Usually this is not the limiting factor to administration set use. Most drip chambers are made from polypropylene, PVC, or polycarbonate but do not contain plasticizers.

Occasionally, Taxol solution has been observed leaking from the pressure equalization vent hole near the drip chamber of administration sets used to infuse solutions from glass bottles or noncollapsible fluid containers. Although a definitive explanation for this occurrence is not apparent, it may be related to the surfactant properties of the Taxol vehicle. Taxol administration requires the use of an in-line filter due to possible fiber and particulate formation over time. While fiber formation may not indicate loss of Taxol potency, solutions with excess particles should not be used. By far, the most tested filters are the IVEX-2® and IVEX-HP® filter sets (Abbott, North Chicago, Ill.). Both of these filters contain a cellulose acetate/Teflon® 0.22-micron filter membrane encased in a nonplasticized, rigid PVC (or polyester) housing attached to a 15-inch-long plasticized PVC extension set. Although the extension set does contain DEHP plasticizer, leaching studies conducted by BMS have demonstrated that the quantity of DEHP extracted from the IVEX-2® tubing is reasonably low (15.7 to 18.3 mg) during a simulated 24-hour infusion (S. Evans, unpublished observations, 1992). This amount is approximately the same as that contained in a unit of whole blood stored in a PVC container for 21 days (about 25 mg) (19). The integral extension set can be connected directly to the patient's intravenous access site, obviating the need to attach additional extension sets between the administration set and the patient. Other in-line filters should be used only after their compatibility with the Taxol vehicle has been confirmed. The filter material, the composition of the fluid contact surfaces, and the adhesives used to connect the various parts of the filter device should be considered.

If Taxol is to be administered through a central venous access catheter, the catheter's composition must be considered. A multitude of venous access devices are available for the administration of chemotherapy. These include the centrally placed tunneled and nontunneled catheters, peripherally inserted central venous catheters, long-term peripheral catheters, and implanted ports, which are attached to central venous catheters. The majority of the catheter material is either silicone (Hickman®, Cook-TPN®, Groshong®, Quinton®, Centrasis®, Intrasil®) or polyurethane (Harborin®, Arrow®, Burron®); however, some contain PVC (Intra-Cath®). Materials in the reservoir of the implantable port system include titanium (Davol Hickman Titanium®, Port-A-Cath Titanium®, P.A.S. Port®), stainless steel (Port-A-Cath Stainless Steel®, Quinton®), or polysulfone, a rigid plastic that does not contain plasticizers (Vital Port®, Infuse-A-Port®), and therefore does not present problems for Taxol infusions.

For practical purposes, it may be unavoidable to introduce some plasticized PVC tubing into the fluid pathway. For instance, many institutions require that all chemotherapy be piggy-backed into a freely flowing intravenous line usually containing 5% dextrose injection or 0.9% sodium

chloride injection. Because many available nitroglycerin sets do not incorporate side-ports, it is necessary to use a conventional PVC administration set for this auxiliary line. If this practice cannot be circumvented, it is recommended that the most distal side-port be used to connect the Taxol infusion to this primary line.

Some institutions routinely attach a short extension tubing to the needle entering implantable central access devices to facilitate connecting intravenous lines to the implanted port. For this situation, a DEHP-plasticized extension set that has been demonstrated to be Taxol-compatible can be used, or alternatively, a micro-bore, polyolefin-lined extension tubing set (e.g. Polyfin®-Extension Set, Minimed Technologies, Sylmar, Calif.) may be substituted. TOTM-plasticized PVC extension tubings and implanted port-needles with integrated extension sets (e.g. LifePort® Infusion Set, Strato Medical, Beverly, Mass.) are now readily available; many of these sets have been demonstrated to be compatible with Taxol administration. In addition, some "needleless" implanted port access systems (e.g., SureCath® Port Access Catheter, Ivion Corp, Broomfield, Colo.) have recently become available that incorporate very small DEHP-plasticized tubing segments and may be used for Taxol administration.

When circumstances arise that may necessitate the introduction of additional tubing into the fluid pathway, a non-DEHP set or a tubing set that has been specifically tested for Taxol compatibility should be used, or if these are unavailable, the shortest DEHP-plasticized tubing may be considered.

Taxol Compatibility with Other Medications

Patients receiving Taxol may also be receiving other medications that require intravenous administration. Often this patient population has limited venous access; therefore, questions may arise about the compatibility of Taxol with other medications either mixed with Taxol or administered concurrently via a Y-site injection port. No studies have examined the compatibility of other drugs admixed with Taxol. Trissel et al. evaluated the turbidimetric and visual compatibility of 59 drugs in a model simulating Y-site injection (23,24). None of the drugs tested with Taxol produced precipitation, color change, or gas production. However, the authors report that four drugs (chlorpromazine, hydroxyzine, methylprednisone, and mitoxantrone) caused a decrease in turbidity and one drug (amphotericin B) increased the turbidity. The authors caution that turbidimetric and visual compatibility do not ensure chemical compatibility. Therefore, it is prudent to follow the NCI recommendation that no other agent be infused through a line where Taxol is being administered until additional chemical compatibility information is available (25).

Toxicities Associated with Taxol Administration

Myelosuppression was the major dose-limiting toxicity in the phase I trials of Taxol (26-29). An unexpectedly

high incidence of serious hypersensitivity reactions was also noted in phase I studies. It is not clear whether the hypersensitivity reactions were related to the Cremophor EL vehicle or to the drug. Studies have shown that the Cremophor EL vehicle induces histamine release and hypotension in dogs within 10 minutes of administration (30). However, Cremophor EL has been used for the intravenous administration of several other antitumor drugs including didemnin B, echinomycin, and teniposide (25,31). Cremophor EL is also used as an intravenous vehicle for the administration of miconazole, an antifungal agent, as well as for the immunosuppressive agent cyclosporin A (32,33). Significant quantities of Cremophor EL may be administered (e.g., up to 20 to 40 mL per day for up to 30 days with miconazole) with these drugs (34). Only occasional serious hypersensitivity reactions have been associated with the administration of these agents (30,35,36).

In January 1985, the NCI sent a letter to all phase I investigators using Taxol, directing them to increase the duration of Taxol infusions and to pretreat all subjects with antihistamines (both H₁ and H₂ blockers) and steroids, a regimen similar to that given to patients who are allergic to radiographic contrast dyes (37). The incidence of hypersensitivity reactions subsequently decreased. Because the infusion duration was increased and pretreatment medications were added at the same time, it was not possible to determine whether infusion rate or pretreatment was the important factor.

BMS has recently sponsored a randomized clinical trial in patients with refractory ovarian cancer in Canada and Europe to address the safety of a 3-hour infusion following the pretreatment regimen. Preliminary analysis indicates that when premedications are used, the incidence of hypersensitivity reactions is similar when using either a 3- or 24-hour infusion (38). Final results are pending.

When the high incidence of serious hypersensitivity reactions became apparent in the early studies, investigators at Johns Hopkins Cancer Center began cardiac monitoring for all patients receiving Taxol (39). Cardiac disturbances were noted during Taxol infusions. Asymptomatic bradycardia was observed in 29% of ovarian cancer patients treated in a phase II study (8). More serious cardiac rhythm abnormalities, including A-V block of various degrees, left-bundle branch block, ventricular tachycardia, and manifestations of cardiac ischemia, were reported in 5% of patients (7 out of 145) (39). The cardiac effects of Taxol are discussed elsewhere in this monograph (p. 117) by Arbuck et al.

NCI, as the sponsor of the exemption for an investigational new drug for Taxol, is required to report all adverse drug reactions to the FDA. NCI has received two reports of toxicity related to extravasation of Taxol (Cancer Therapy Evaluation Program, NCI, data on file, 1992). The first case was a 44-year-old female receiving Taxol for refractory ovarian cancer. Near the end of her infusion there was an infiltration at the site of her implanted port in the left chest wall. The site was erythematous and slightly edematous. The needle was reinserted and the

infusion completed. Treatment included cold compresses and silver sulfadiazine cream. One week later there was a 4-cm × 4-cm ulceration. The ulceration healed over a period of 1 month. Three months later a small crescent-shaped scar remained. The second case was a 67-year-old female being treated for ovarian cancer. The Taxol was being infused over 24 hours via an implanted administration port. Approximately 17 hours into the infusion the patient complained of burning and redness around the port. The infusion site was changed. Warm compresses and then cold compresses were applied, and a course of oral cephalexin was given. The site remained irritated and erythematous 3 months later, and after 7 months an area of induration remained. The port was then removed. In both of these cases, the infiltration occurred when the needle was dislodged from a subcutaneously implanted administration port; conservative treatments were used, and the injury healed slowly. In the case where ulceration occurred, the needle was reinserted, and the infusion continued via the port after the infiltration was noted. At this time there is no recommended local antidote for Taxol extravasations. On the basis of the very limited information available, conservative therapy is recommended (40). Additionally, if an infiltration occurs, the administration site should be changed even if the drug is being infused through an implanted port.

Other toxicities reported in phase I/II studies include almost universal alopecia, mild nausea and vomiting, stomatitis, mucositis, diarrhea, peripheral neuropathy, myalgia, and arthralgia.

CONCLUSION

Taxol is an interesting new antineoplastic agent with a unique mechanism of action that is formulated in a Cremophor EL/ethanol vehicle. It has recently been approved for the treatment of metastatic ovarian cancer after failure of first-line or subsequent chemotherapy. Initial studies have indicated activity in breast cancer, but additional research is needed to clarify Taxol's role in this disease. Activity has also been noted in lung cancer and head and neck cancer. Research continues to elucidate the activity in these and other cancers.

The current Taxol formulation presents a number of concerns including stability, filtering requirements, use of nonplasticized solution containers and administration sets, and compatibility with indwelling catheters. Efforts continue to develop new formulations and new analogues that may be soluble in aqueous vehicles, thereby eliminating the problems associated with the Cremophor EL-ethanol solvent system. Current data indicate that Taxol may be diluted in either NS, D5W, D5NS, or D5W-R. When prepared in these diluents, Taxol solutions (0.3 to 1.2 mg/mL) are physically and chemically stable up to 27 hours at room temperature and ambient light. Taxol must be prepared in glass, polyolefin, or other plasticizer-free containers because of leaching of DEHP plasticizer from PVC bags and intravenous tubing by the Cremophor EL

vehicle in which Taxol is solubilized. In-line filtration is necessary for administration of Taxol solutions. Although particulate formation may not indicate loss of drug potency, solutions exhibiting excessive (e.g., grossly apparent) particulate matter formation should not be used. Taxol should be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as most administration sets that are used to infuse parenteral nitroglycerin or fat emulsions. If unavoidable, the introduction of any plasticized PVC tubing into the fluid pathway, such as the tubing connected to a filter set or an extension set, should be kept at the very minimum. Taxol is compatible with indwelling silicone or polyurethane central catheters and implantable ports made of titanium, stainless steel, or polysulfones. Until chemical compatibility studies are completed, it is recommended that no other agent be mixed with or infused into a line where Taxol is being administered.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Nursing Management of the Patient Receiving Taxol Therapy

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Taxol is an important new antitumor agent with demonstrated efficacy in ovarian and breast cancer. Toxicities identified, including cardiac, hypersensitivity reactions, and neurologic, require careful nursing assessment for management. Additional toxicities may be identified as Taxol is combined with other chemotherapeutic agents. Studies to determine the most effective dose and schedule are ongoing. The current evaluation of this new drug presents an important opportunity for nurses to contribute to its development through both clinical and research endeavors. Such contributions will facilitate the optimal nursing care of patients treated with Taxol. [Monogr Natl Cancer Inst 15:149-154, 1993]

Taxol¹ is a plant product that is being extensively evaluated as an antineoplastic agent. This novel alkaloid compound has a complex structure that was identified by Wani et al. in 1971 (1). Unlike the vinca alkaloids (vincristine, vinblastine), which inhibit the assembly of microtubules, Taxol promotes microtubule polymerization and inhibits depolymerization (2-5). In this way, Taxol acts as an inhibitor of cell replication, blocking cells in the G₂ and M phase of the cell cycle (6). This activity interferes with the normal functioning of the mitotic spindle, preventing the cell from completing mitosis (7). Taxol is isolated from the bark of the western yew (*Taxus brevifolia*), a small evergreen native to the Pacific Northwest (8). The process of extraction is lengthy and requires a large volume of raw material to produce relatively small amounts of the drug. Intense efforts are ongoing to produce a synthetic version of the drug and to obtain it from renewable sources such as needles of trees.

Following preclinical toxicity studies, Taxol entered phase I clinical trials in 1984. Initially, the ability to conduct these phase I studies was limited by the supply of the natural product and the poor aqueous solubility of Taxol. After phase I studies were initiated, they were almost curtailed because of the high incidence of hypersensitivity reactions (HSRs) (9). To reduce the occurrence of HSRs, a premedication regimen of corticosteroids, antihistamines, and H₂-antagonists was added. In addition, infusion times were lengthened in later studies because the HSRs had occurred when Taxol was given as a short (less than 6 hours) intravenous infusion (9-11). Phase II studies were then undertaken with the 24-hour continuous infusion and the premedication regimen. This schedule was chosen because of the low incidence of HSRs and because responses were seen in phase I studies (12). More recent data indicate

that neither the dose nor the schedule affect the frequency or severity of the HSRs when steroid, antihistamine, and H₂ receptor antagonist premedications are administered (13).

Studies have determined that the maximally tolerated dose of Taxol administered by 24-hour infusion every 3 weeks is 200 mg/m² to 250 mg/m² in patients without extensive prior therapy and 135 mg/m² in heavily pretreated patients. Currently, a dose of 175 mg/m² to 200 mg/m² without granulocyte-colony stimulating factor (G-CSF) is often administered, and 250 mg/m² can be administered with G-CSF. On the basis of information available at the time of Food and Drug Administration (FDA) review of Taxol, the FDA approved a dose of 135 mg/m² for patients with ovarian cancer after failure of first-line or subsequent chemotherapy.

Broad phase II studies are ongoing with Taxol in both solid tumors and hematologic malignancies. Phase III studies are currently being conducted in both breast cancer and ovarian carcinoma.

Important questions remain in establishing the optimal use of Taxol. First, it must be determined whether there is a dose-response relationship for Taxol because responses occur at lower doses as well as at the maximally tolerated dose. Second, studies are ongoing to determine the optimal schedule of administration. Third, the activity of Taxol in combination with other active agents for specific diseases needs to be determined. Phase I studies of such combinations are ongoing. Fourth, the impact of this particular chemotherapy on the patient's quality of life must be evaluated. Prospective studies of the effects of Taxol treatment on various quality-of-life end points, including physical function, symptom distress, and psychological state, are in progress for women with advanced breast cancer (14).

TREATMENT AND MANAGEMENT OF TOXICITIES

As clinical trials of Taxol proceeded and were evaluated, the clinical toxicities of Taxol were identified. One of the more striking side effects of Taxol has been the severe allergic reactions (HSRs). Their incidence has been greatly reduced with the use of premedications that have permitted clinical trials to continue (15). Other side effects of Taxol have been observed and are grouped into the following categories: cardiac, hematologic, neurologic, gastrointestinal, and miscellaneous. (See Table 1.)

HSRs typically occur within the first 10 minutes of the first or second dose of Taxol. However, an HSR is known

*See "Notes" section following "References."

Table 1. Toxicities reported with Taxol

<i>Hematologic</i>	<i>Neurologic</i>
Leukopenia/neutropenia	Mood alterations
Anemia	Sensory (taste)
Thrombocytopenia	Peripheral neuropathy
	Seizures
<i>Gastrointestinal</i>	<i>Cardiac</i>
Stomatitis	Hypotension
Mucositis	Arrhythmia
Diarrhea	Sinus bradycardia
Nausea/vomiting	Ventricular tachycardia
Decreased appetite	Heartblock
Pharyngitis	Myocardial infarction
<i>Hypersensitivity Reactions</i>	<i>Miscellaneous</i>
Dyspnea	Alopecia
Hypotension	Fatigue
Angioedema	Myalgias
Urticaria/rash	Arthralgias
Facial flushing	Nail changes
Bronchospasm	Venous irritant
Pruritus	Light-headedness
	Myopathy

to have occurred as much as 12 hours after the completion of a patient's first 6-hour infusion. Symptoms of HSRs include dyspnea, bronchospasm, blood pressure changes, angioedema, urticaria, rash, flushing, and even nausea, vomiting, abdominal pain, lower extremity pain, and fever (9). The cause of these reactions remains unclear. HSRs similar to those seen with Taxol administration have been reported with the administration of iodinated radiocontrast dyes (9). The same mechanism of tissue or basophil-released histamines is believed to cause Taxol-induced HSRs (16). Interestingly, the cremophor vehicle in which Taxol is formulated is associated with HSRs. Animal studies indicate that cremophor can trigger histamine release, thereby causing an acute allergic reaction (17).

Because of the severity and frequency of Taxol-induced HSRs, the administration of premedications consisting of dexamethasone, diphenhydramine, and an H_2 -histamine antagonist is recommended by the National Cancer Institute (NCI). (See Table 2.) A similar course of premedications has been effective in reducing iodinated radiocontrast dye reactions. These premedications are not completely protective, and HSRs have occurred in patients who have received this prophylactic drug regimen. However, minimal risks are associated with these premedications, and, since the incidence of severe HSRs is significantly decreased, their use is warranted (9). As already mentioned, initial NCI-sponsored phase II trials combined the premedication regimen with a 24-hour continuous intravenous infusion. Preliminary results from a recently completed European/Canadian trial that randomized refractory ovarian cancer patients to 3-hour and 24-hour infusion schedules with Taxol doses of 135 mg/m² and 175

Table 2. Taxol premedications

Dexamethasone, 20 mg, po 14 hours and 7 hours prior to Taxol infusion*

Cimetidine, 300 mg, IV and diphenhydramine, 50 mg, IV 30 minutes prior to Taxol infusion*

*If the Taxol infusion is delayed by ≥ 2 hours, consideration should be given to repeating the premedications prior to starting the infusion.

mg/m², respectively, indicate that Taxol can be safely given at these doses and schedules (13).

Timely administration of premedications is an important nursing issue. Consideration should be given to the establishment of guidelines for the repeat administration of premedications when the Taxol infusion is delayed. For example, at the NCI Clinical Center, if initiation of the Taxol infusion is delayed by more than 2 hours in breast cancer protocols, the premedications are repeated prior to the infusion. Emergency medications and equipment to treat anaphylaxis must be readily available. Patients should be instructed regarding the symptoms of acute allergic reactions and the importance of promptly reporting such symptoms. A physician should be available for the first 30 minutes of the infusion. A patent intravenous (IV) site (either peripheral or central venous) is required for the Taxol infusion. Frequent monitoring of the IV site through which Taxol is infused is needed because the cremophor vehicle in which Taxol is formulated is a known venous irritant (18; Robert T. Dorr, Ph.D., R.Ph., Arizona Cancer Center, personal communication, 1992). Because of these venous irritant properties, both peripheral and central venous access sites of infusion should be carefully monitored.

Taxol must be administered via polyethylene-lined nitroglycerin tubing because cremophor leaches plasticizers from conventional tubing made of polyvinyl chloride. A 22- μ m filter must be placed on the IV tubing to remove any Taxol particles that may develop following the preparation of the drug (18,19). Specific guidelines to ensure frequent vital sign monitoring during the infusion should be established, particularly during the first hour when an HSR is most likely (9,18). If a Taxol-induced HSR does occur, the drug should be immediately discontinued and IV fluids started while the physician is called. Emergency medications should be administered as ordered, and the patient should be closely monitored, particularly for air-exchange difficulties. Following an acute HSR, additional psychological support may be indicated.

Cardiac disturbances are another unusual and uncommon side effect of Taxol. Various cardiac arrhythmias have occurred during Taxol administration including ventricular tachycardia, atrioventricular conduction block, bundle branch block, and bradycardia (20). Additional cardiac disturbances that have occurred include bigeminy, trigeminy, premature ventricular contractions, chest pain consistent with cardiac ischemia, and hypotension (20). Syncope has also rarely occurred. Of these toxicities, asymptomatic bradycardia is the most common (20).

However, in a review of 403 patients who received Taxol at doses of 135 mg/m² to 250 mg/m² over 3 hours or 24 hours, there was only a 1.5% incidence of severe cardiovascular toxicities. (Data on file, Bristol-Myers Squibb Company, Princeton, N.J.) Generally, cardiac abnormalities resolve when the infusion is stopped, but they may recur upon reintroduction of the drug (20).

At present, the cause of these relatively uncommon cardiac disturbances is not fully understood. Currently, many Taxol studies exclude patients who would not be able to tolerate bradycardia. These patients include those with a history of congestive heart failure or angina and those who have had a recent myocardial infarction (within 6 months). In addition, patients who are on medications that are known to alter cardiac conduction such as digoxin, beta blockers, and calcium channel blockers have been excluded from most studies (21). Further evaluation may help determine if these patients can be treated safely.

Prior to treatment, baseline vital signs and an electrocardiogram should be obtained and the results reviewed. The patient's chart must be reviewed for information regarding use of cardiac and antihypertensive medications, as well as for a history of cardiac disturbances. During the infusion, heart rate and blood pressure are frequently monitored, and the patient should be instructed to report any unusual symptoms immediately. Routine careful observation of fluid and electrolyte status is also recommended (18,20).

Myelosuppression is the most frequently reported dose-limiting toxicity in Taxol clinical trials (17). Neutropenia may develop before day 10 and usually resolves by day 21 of the cycle with or without hemopoietic growth factors. Use of growth factors may reduce the duration of myelosuppression, thus enhancing recovery of the granulocyte counts.

Ongoing Taxol studies incorporate growth factors into the treatment regimen, but it is not known whether their use is associated with increased efficacy. Prior irradiation of marrow-containing bone and/or previous treatment with chemotherapy may make a patient more susceptible to the myelosuppressive effects of Taxol. Data suggest that the neutropenia associated with Taxol is not cumulative (17). Anemia and thrombocytopenia are rare potential adverse effects of Taxol administration (17).

Nursing actions regarding neutropenia center around patient education. The definition of neutropenia absolute granulocyte count ([AGC] greater than 500 or 1000 per μ L) should be explained to the patient as well as special precautions they should follow while they are at risk of neutropenia. (See Table 3.) Complete blood counts with differential should be obtained at least weekly unless there is a specific indication to obtain them more frequently. The patient should be informed when he or she becomes neutropenic so that these precautions can be implemented (Table 3). When the neutrophil count has recovered to an AGC greater than 500 per μ L, the risk of infection is reduced and the patient may resume his or her normal activities.

Patient education should also include the signs and symptoms of anemia and thrombocytopenia. The patient

Table 3. Neutropenia precautions*

- When neutropenic, the temperature should be monitored 3 to 4 times per day and the physician notified if the temperature is 101.3°F (38.5°C) once in a 24-hour period or 100.4°F (38.0°C) three times in a 24-hour period.
- Tylenol (acetaminophen) and Tylenol-containing products as well as aspirin (acetylsalicylic acid) and aspirin-based products should be given only on the physician's advice.
- Any sign or symptom of infection including fever, redness, swelling, tenderness, or drainage, particularly in mouth or peri-rectal areas, or at the entry site of a central venous catheter, should be promptly reported to the physician.
- Good skin and mouth care should be stressed.
- Exposure to animal waste should be avoided.
- Large crowds and sick children should be avoided. Hot tubs and jacuzzis or any activity that could expose the patient to unusual pathogens should be avoided.
- Immunizations and injections should be avoided (if possible) as well as enemas, rectal thermometers, and suppositories. Women should avoid tampons, vaginal suppositories, or douches.
- Fresh fruits and vegetables should be peeled, and all raw or uncooked food avoided.
- Precautions should be taken to avoid any injury to the skin, and if such an injury occurs, the site should be frequently monitored for signs of infection.

*Adapted from the *Living with Cancer* series. Cancer Nursing Service, National Institutes of Health, Clinical Center, December 1990.

should be instructed to report fatigue, dizziness, or shortness of breath. Symptomatic anemia is treated with red blood cell transfusions. Similarly, the patient should promptly report any unusual bruising, bleeding, or petechiae because these symptoms may require a platelet transfusion.

Abnormal microtubule function within neurons and Schwann cells is a possible cause of the neurotoxicity associated with Taxol (17,22). The administration of higher doses of Taxol (greater than 170 mg/m²) is frequently associated with peripheral neuropathy, which is dose limiting at 250 mg/m². Repeated administration of lower doses can also induce sensory changes. Early symptoms include a burning pain in the feet that may progress to a glove-and-stocking distribution of numbness or paresthesia, a decrease in perioral sensation, and a decrease or loss of deep tendon reflexes. Symptoms may occur quickly (with high doses of Taxol) or develop more slowly due to a cumulative effect of the drug. When neuropathy develops, it can frequently be managed by awaiting recovery to grade 1 toxicity and then treating with a lower dose. Termination of therapy is rarely required. Symptoms generally resolve within several months of completing the therapy (17).

Prior treatment with a neurotoxic chemotherapy agent (i.e., cisplatin) may predispose a patient to develop

neuropathy. A history of alcohol abuse or diabetes may also make a patient susceptible, and patients with these conditions should be monitored closely (17,23). The patient should be instructed to report any sensory changes or any difficulty with tasks such as buttoning a shirt. If peripheral neuropathy does develop, the patient should be taught proper foot and skin care as well as the need for caution in skin-testing the temperature of liquids. The patient should be reminded that neuropathy is usually temporary and will generally resolve once treatment is completed.

Gastrointestinal toxicities from Taxol have been observed infrequently. With Taxol doses greater than 315 mg/m², severe mucositis with ulcerations lining the oral mucosa and esophagus occurred in one phase I study in leukemia patients (17). The incidence was low in most solid tumor trials using lower Taxol doses (17). Oral and esophageal ulcerations may begin as early as 3 days after treatment and generally resolve within 5 to 7 days of the onset of symptoms (17). Ulcerations may be painful, and the patient must be carefully monitored for adequate pain control. With severe pain, narcotic medication may be needed.

Dysphagia frequently accompanies mucositis, and the patient must be carefully assessed for difficulty with fluid intake. Poor fluid consumption can lead to dehydration, and the possible need for intravenous fluids must be carefully evaluated. Sodium bicarbonate and microbicidal mouth rinses may lessen the severity of mucositis when it occurs. Mild nausea, vomiting, and diarrhea have also been associated with Taxol administration, and these should be treated symptomatically (17).

Myalgias and arthralgias are also side effects of Taxol therapy and are more common at high doses (17,24). Symptoms may develop within 48 to 72 hours of treatment and generally resolve within 1 week. Most commonly affected sites are the paraspinal muscles, pelvis, and arm and leg joints (17,24). These symptoms vary in severity, and narcotic medications may be required for adequate pain control. The administration of hematopoietic growth factors may intensify the discomfort.

Other side effects include complete alopecia (loss of all body hair), which occurs in all patients 2 to 3 weeks after treatment with Taxol doses above 135 mg/m² (17). Hair growth generally resumes 6 to 8 weeks after termination of therapy. As discussed earlier, Cremophor is a venous irritant and can be locally toxic to the skin. Taxol that infiltrates tissue around a peripheral IV site can cause erythema, pain, and induration (17,18). Generally, a cold compress followed by a warm compress applied to the site may reduce discomfort. Skin ulceration has occurred with Taxol infiltration. However, the adverse effects caused by infiltration resolved with conservative management (CTEP Adverse Drug Reaction Data Base, NCI, data on file, 1993).

Mild-to-moderate fatigue may develop within 24 hours of Taxol administration and is dose dependent. Nursing actions should center around informing the patient of the need for frequent rest periods and curtailed activities of

daily living when needed. Symptoms of fatigue may continue for several days. Additional side effects of Taxol therapy include taste changes and nail changes with ridging and discoloration.

Phase I clinical trials of Taxol in combination with other chemotherapeutic agents, including doxorubicin or cyclophosphamide, are ongoing. The toxicities that occur when Taxol is given in combination with these or other agents may be unique to the doses and combination of Taxol and the specific agent. It is important that the patient receiving Taxol in combination with another agent be regularly assessed for new or severe side effects, and these toxicities should be promptly treated.

NURSING IMPLICATIONS

As with any new cancer therapy being evaluated, it is important for nurses to develop standards of care to ensure the safe and responsible care of the patient receiving the new treatment. Nurses will need to develop policies and procedures for the administration of Taxol including IV administration with the correct tubing and filters, timing of premedications and guidelines for their use, appropriate schedule of vital signs to monitor for HSRs and cardiac toxicities, documentation of side effects and their management, and the development of specific patient education strategies. Nurses may also be instrumental in designing and implementing research studies that will describe the symptomatic, psychosocial, and financial impact of this treatment as it moves from the clinical trials to much broader usage.

PATIENT EDUCATION

Patient education regarding Taxol therapy should begin during the first interaction with a patient. Education is especially important for patients using Taxol because many patients have unrealistic expectations of the drug. Patients may not understand that clinical studies are under way to resolve unanswered issues including evaluation of the optimal dose and schedule and determination of Taxol's efficacy. If the patient is receiving Taxol as part of a clinical trial, the goals of that trial must be explained to the patient during the informed-consent process. Many patients have difficulty understanding the significance of a phase I, II, or III study, and the NCI patient information booklet *What Are Clinical Trials All About?* may be helpful (25). It is important to determine what the patient understands about Taxol and to correct any misconceptions he or she may have from information received through the media and other sources. The patient should be informed about other treatment options that are available. If possible, the patient should be encouraged to have someone accompany him or her during this initial teaching visit to help formulate questions and retain accurate information. Written information is always helpful.

A careful description of what to expect with Taxol administration should be given, with special attention

given to the setting in which the therapy will be administered. Taxol, by 24-hour infusion, may be given in an inpatient oncology unit or a special telemetry or monitoring unit, or it may prove possible to administer it in an outpatient setting. Taxol, by 3-hour infusion, has been administered safely to outpatients (13). The toxicities of the drug and their management should be carefully reviewed with the patient; frequent reinforcement will be required as side effects occur. Because new side effects are possible when Taxol is combined with other chemotherapeutic agents, patients should be told to communicate any new signs or symptoms. Patients also need to understand the importance of having their blood counts checked frequently because myelosuppression is a common toxic effect. It is important that patients know how their disease will be evaluated for response and at what time intervals specific tests or remeasurements will occur. Patients should be encouraged to bring someone with them when they have their first reevaluation examination because this often is a time of anxiety. Information regarding the duration of Taxol therapy should be discussed initially, including reasons for early discontinuation of therapy.

Issues regarding insurance coverage and reimbursement should be discussed prior to the initiation of Taxol treatment. Insurance coverage may vary by plan and may depend upon the indication for which Taxol is being used and whether the patient is being treated in a clinical trial. Patients should be encouraged to talk with their insurance carriers so they are aware of what will be covered prior to the initiation of therapy.

CONCLUSION

Taxol is a new and important antimicrotubule agent. The initial scarcity of the drug's natural source presented enormous obstacles to its development. In addition, the identification of HSRs and cardiac arrhythmias as two unusual treatment-related toxicities presented important clinical management challenges. Efficacy has been demonstrated in both ovarian and breast cancer. Ongoing clinical trials are being conducted to evaluate the activity of Taxol in other malignancies and to determine the most effective dose and schedule. Careful nursing assessment is important for the management of neurologic, hematologic, and cardiac toxicities and HSRs. The continued evaluation of this drug includes important opportunities for nurses to contribute to the clinical knowledge and optimal nursing care of patients treated with Taxol.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Taxol in Epithelial Ovarian Cancer

Carlos Caldas, William P. McGuire III*

Epithelial ovarian cancer is the fifth most common cause of cancer death in women. The management of patients with advanced disease involves surgery followed by platinum-based chemotherapy, but most patients will have either residual or recurrent disease. Salvage therapy in these patients is poor, with response rates less than 20%. Taxol, a new antineoplastic agent, was first noted to have activity in platinum-resistant ovarian cancer in a phase I study. Since then, response rates of 20% to 35% have been noted in several phase II studies involving hundreds of patients. Major toxicities include neutropenia and peripheral neuropathy. Taxol dose escalation with granulocyte-colony stimulating factor support, and Taxol in combination with cisplatin, have been tested and shown to be feasible. Intraperitoneal administration of Taxol is possible and appears advantageous from a pharmacokinetic perspective. A phase III study of Taxol and cisplatin in suboptimal disease was completed, and toxicity data show that Taxol administration is safe in a multi-institutional setting. Planned clinical development of Taxol includes use in less bulky stage III disease and dose escalation in platinum-resistant disease. Taxol has already become a major treatment of platinum-resistant disease. Further investigation will determine its role in the overall management of ovarian cancer. [Monogr Natl Cancer Inst 15:155-159, 1993]

Epithelial ovarian cancer is the fifth most common cause of female cancer death and, of the female pelvic malignancies, the most common cause of death (1). The reasons for this lethality are multifactorial, but the fact that 75% to 80% of patients present with advanced-stage disease (stages III and IV in the International Federation of Gynecology and Obstetrics [FIGO] staging system) is likely primary (2).

Surgery is the initial therapy of ovarian cancer and is performed to provide adequate staging and cytoreduction. Despite optimal surgical therapy, more than 85% of patients will require some form of postoperative adjuvant treatment. Persistent disease will be found during second-look surgery in 50% to 60% of patients in clinical complete remission (CR) at the completion of primary therapy, and recurrent disease will develop in 35% to 45% of patients with pathologically negative re-exploration (3). In early stage disease (FIGO stages I and II), only patients with high-grade tumors or stages IC and II should be considered for adjuvant therapy with intraperitoneal ^{32}P , although even this recommendation is controversial (4,5).

Postoperative therapy in advanced-stage disease (FIGO stages III and IV) involves chemotherapy, the possible exception being the stage III patient with no residual disease after surgery who can be treated as effectively with whole abdominal irradiation (6). Clinical research has established cisplatin-based therapy as most effective, with response rates of 70% to 80% and 20% to 50% pathologic CRs. Despite these results, the impact on survival has been marginal (7).

Current controversies in the treatment of advanced ovarian cancer include the role of intraperitoneal chemotherapy as salvage or primary treatment and the efficacy of cisplatin dose intensity (8-12).

The outcome of 100 hypothetical patients (all stages) receiving state-of-the-art therapy summarizes the present status of ovarian cancer: 35 patients will be alive at 5 years, 75 have advanced disease at presentation, and, after completion of primary therapy, only 25 will be in pathologic CR, and from this group eight to 12 will relapse and eventually die (13).

When cisplatin first became available, response rates of 30% or more were seen in patients with alkylating agent refractory disease (14). Unfortunately, treatment of platinum-resistant disease is not nearly as successful, with most agents (hexamethylmelamine, ifosfamide, doxorubicin) having response rates of less than 20% (7,15-17).

During a phase I study of Taxol,¹ a drug isolated from the bark of the Pacific yew tree (*Taxus brevifolia*) with a novel antimicrotubule mechanism of action, a patient with heavily pretreated and cisplatin-resistant ovarian cancer had a dramatic and prolonged response (18). This very unusual response was the basis for initiating a series of phase II studies that have since confirmed Taxol as an active drug in the treatment of advanced ovarian cancer, including platinum-resistant disease.

In this manuscript, we review the published phase I and II studies of Taxol therapy in ovarian cancer, report early results of studies recently completed or nearing conclusion, and discuss the rationale for recently activated or planned clinical trials. Finally, we offer our view of the current role of Taxol in the therapeutic armamentarium of ovarian cancer and what prospects we see for future clinical development.

SINGLE-AGENT TAXOL

Published Phase II Studies

Results of five phase II studies of Taxol treatment in advanced ovarian cancer have been reported. These stud-

*See "Notes" section following "References."

ies, involving a total of 110 patients evaluable for response, demonstrated an overall response rate (CRs plus partial remissions [PRs]) of 30%.

The Johns Hopkins study (19) enrolled 47 patients with progressive and drug-refractory ovarian cancer, of whom 45 were evaluable for toxicity and 40 for response. Patients had received a mean of 2.7 previous chemotherapy treatments, all had been treated previously with cisplatin, and 32 of the 47 patients (25 of 40 evaluable) were refractory to cisplatin, as defined by either tumor growth while receiving cisplatin or recurrence of tumor within 6 months of completion of a cisplatin-containing regimen. The starting doses of Taxol were 250 mg/m² and 200 mg/m² given over 24 hours every 3 weeks in patients with single prior chemotherapy and two or more prior chemotherapies, respectively. This dosing regimen was reduced to 200 mg/m² and 170 mg/m², respectively, after severe hematologic toxicity was noted early in patient accrual; in some heavily pretreated patients further reductions to 135 mg/m² and 110 mg/m² were performed secondary to grade 4 neutropenia. There were no significant differences regarding age, performance status, or amount of previous therapy between responders and all enrolled patients. Exclusion from response analysis was caused by early death (four patients), no treatment received (one patient), wrong diagnosis (one patient with Krukenberg metastasis from gastric cancer), and no follow-up (one patient). Response rate was 30% (confidence interval [CI] 16% to 44%) of which one was a pathologic CR and 11 were PRs, with response durations of 2 to 15 months (median, six). There were seven additional patients with minor responses (reduction of indicators by 25% to 49% without appearance of new lesions) who reported resolution of clinical symptoms. The number of courses to attain a response varied from one to six (mean, three), and there was no clear correlation between the received dose of Taxol and the likelihood of response. The main toxicity was hematologic, with 57% of the courses complicated by grade 4 neutropenia (40 of 41 patients had at least one episode) and 20% by mild anemia or thrombocytopenia. Febrile neutropenia occurred in 21 of 281 courses (14 patients). Mild (grades 1 and 2) peripheral neurotoxicity was seen in 33% of courses (44% of patients); however, this was not clearly drug related, because most patients had pre-existing platinum neuropathy. Asymptomatic bradycardia was noted in 13 patients, and alopecia was universal. A syndrome of arthralgias and myalgias occurred in 27% of the courses.

The Gynecologic Oncology Group (GOG) study (20) accrued 48 patients with ovarian cancer previously treated with cisplatin-based therapy, and 27 had platinum-resistant tumors (as defined above). There were 43 patients evaluable for toxicity and 41 for response. Taxol was administered at a dose of 175 mg/m² by 24-hour infusion every 3 weeks. The response rate was 36% (five CRs and 10 PRs), and the main toxicity was hematologic (65% had 2000 white blood cells/cm³).

Finally, in the Albert Einstein study (21) 31 patients with measurable advanced ovarian cancer, 30 of whom had received prior chemotherapy, received Taxol, 250

mg/m² by 24-hour infusion every 3 weeks. In 29 evaluable patients, the response rate was 21% (one CR and five PRs). The main toxicities were febrile neutropenia (20 patients) and peripheral neuropathy (requiring dose reduction in six patients).

In the first two studies, where this information is available, the response rate in platinum-refractory disease was a remarkable 27% (14 of 52 patients).

The National Cancer Institute (NCI) sponsored the Treatment Referral Center protocol generated by the demand for Taxol after early reports of activity in refractory ovarian cancer and prior to commercial availability of the drug. Patients with platinum-refractory ovarian cancer failing at least three prior chemotherapy regimens were eligible to receive Taxol (135 mg/m² over 24 hours every 3 weeks). G-CSF was added after cycle 1 for severe and protracted neutropenia or neutropenic fever. As of May 1993, more than 2000 patients had been enrolled. Unaudited data from the first 1000 patients (710 with measurable disease) showed a response rate of 22% (95% CI = 18 to 26%), with 78% incidence of grade 3 or 4 neutropenia and 2% grade 3 to 4 neurotoxicity (29). The response rate in a very large multi-institutional study is similar to outcomes of the prior phase II studies. All patients in this study had platinum-resistant disease, again confirming the significant activity of Taxol in this group.

Dose Intensification of Taxol With Granulocyte-Colony Stimulating Factor Support

The effect of dose intensity on response rate and, more important, on survival is unclear in ovarian cancer (22). Efforts to explore dose intensification with Taxol would have to take into account its myelotoxicity, theoretically preventable with hematopoietic growth factors; potential for serious neurotoxicity; and severe mucositis when used in high doses (23).

Results of a phase I study of Taxol dose intensification with granulocyte-colony stimulating factor (G-CSF) support (10 µg/kg daily subcutaneous) in patients with refractory ovarian cancer have been recently published (24). The dose-limiting toxicity was peripheral neuropathy (dose level of 300 mg/m²), and although neutropenia occurred, it was of brief duration (<5 days) and did not require dose reduction. The three patients who experienced neurotoxicity also had peripheral neuropathy when previously treated with cisplatin. There was no incidence of mucositis greater than grade 1. Based on these results a subsequent phase II study enrolled 46 patients with recurrent ovarian cancer with minimal prior therapy (25). The target Taxol dose intensity was 83.3 mg/m² per week (250 mg/m² every 3 weeks), and patients received 56.3 mg/m² to 93.8 mg/m² per week (median dose intensity, 83.3; mean dose intensity, 79). In the 38 patients evaluable, the response rate was 50% (41% of total patients); no toxicity data were provided.

These two studies show that Taxol dose intensification to 250 mg/m² is feasible. Determining whether Taxol dose intensity has an impact on outcome requires support from well-designed randomized studies.

Dose and Schedule Considerations

The NCI-Canada study prospectively randomized ovarian cancer patients to two dose levels (135 mg/m² or 175 mg/m² every 3 weeks) and to two different infusion schedules (3 hours and 24 hours) of Taxol. Preliminary data suggest that the 3-hour infusion is less myelotoxic and is not associated with a greater incidence of cardiac or allergic events (26). Until the response and survival data are reported, it is premature to conclude that the 3-hour infusion is as safe and as effective as the 24-hour "standard" infusion, especially because the response rate in this study, 19%, is the lowest reported for any phase II trial of Taxol as salvage therapy in ovarian cancer. Nevertheless, the results of this study are potentially important because the short infusion schedule would allow ambulatory administration of Taxol.

TAXOL IN COMBINATION WITH CISPLATIN

Phase I Studies

The activity seen with Taxol in phase II studies in refractory ovarian cancer suggested that the next rational step in its development be in combination with cisplatin, the most active drug in ovarian cancer. In a phase I study from Johns Hopkins, 44 patients with untreated or minimally pretreated solid tumors, including six patients with ovarian cancer, received alternating sequences of Taxol and cisplatin (27). Severe neutropenia occurred in the majority of courses and patients, and grade 4 neutropenia was significantly more common when cisplatin preceded Taxol. Surprisingly, only 27% of patients had either symptomatic or neurometric evidence of neurotoxicity. Five assessable ovarian cancer patients (all with suboptimally debulked stage III and IV) had responses: one patient had a pathologic CR (12 months duration), one patient had a clinical CR but evidence of residual disease at second-look surgery (pathologic partial response lasting longer than 21 months), and the three other patients achieved PRs (lasting 2, 8, and 12 months). In a subsequent phase I study, courses of Taxol followed by cisplatin were given with G-CSF support, and the Taxol dose was escalated (28). The dose-limiting toxicity was severe neuropathy at 300 mg/m². On the basis of the results of these two studies, the sequence of Taxol before cisplatin at doses of 135 mg/m² and 75 mg/m², respectively, was recommended for phase II/III studies, without G-CSF support. Doses of 250 mg/m² and 75 mg/m², respectively, were recommended with G-CSF support.

Phase II-Phase III Studies

Patients with suboptimally debulked ovarian cancer have only a 20% chance of achieving a CR with standard cisplatin-based therapy (7). These patients are obvious candidates for novel therapies that may improve outcome, and the combination of Taxol and cisplatin was therefore considered a study priority in this group of patients.

The GOG has completed enrollment of 410 patients with suboptimally debulked stage III and stage IV ovarian cancer in a phase III study comparing cytoxan (750 mg/m² q21 days to be repeated six times) and cisplatin (75 mg/m² q21 days to be repeated six times), with Taxol (135 mg/m² q21 days to be repeated six times) and cisplatin (75 mg/m² q21 days to be repeated six times). Toxicity data available from 352 patients show the Taxol-containing regimen is associated with more grade 4 neutropenia (79% vs. 61%), more febrile neutropenia (20% vs. 11%), and all of the episodes of cardiac toxicity (N = 7) (29). None of these episodes of cardiac toxicity, however, was of any clinical significance.

The Taxol/cisplatin (Platinol) arm was also associated with more alopecia and peripheral neuropathy, though this latter toxicity was of overall minor clinical importance. Importantly, the Taxol/cisplatin arm generated a higher clinical response rate (79% vs. 62%) and a pathologically negative second look (26% vs. 19%). Median progression-free survival is better in the Taxol/cisplatin arm (18.1 vs. 13.6 months), and survival appears better. No median has been reached yet in the experimental arm. This combination is now being explored in less-advanced disease. Taxol/cisplatin appears to represent a better therapy for advanced ovarian cancer, but ongoing research will better define the role of this combination in future therapy (29).

INTRAPERITONEAL TAXOL

Taxol has a bulky structure and high molecular weight, is metabolized primarily in the liver, and has biologic and cytotoxic effects in tumor cell lines that are potentiated by both higher concentration and longer duration of exposure (23). All these characteristics recommended administration by the intraperitoneal route. A recent phase I study entering 25 patients has been reported (31). The dose-limiting toxicity was severe abdominal pain at doses higher than 175 mg/m². Pharmacologic evaluation demonstrated high Taxol concentrations in the peritoneal cavity, and a very low intraperitoneal clearance of Taxol, such that the peritoneal cavity has about 1000 times more drug exposure than the systemic circulation. Systemic toxicities are minimal at the maximum tolerated dose. Two of the 24 patients with heavily pretreated ovarian cancer had complete resolution of pretreatment ascites, and four others had marked reductions in CA-125 levels.

Further evaluation of intraperitoneal Taxol is needed to determine the optimal dose and schedule. A current study is evaluating lower doses of Taxol given weekly. Future phase II/phase III trials should better define the role of this form of therapy in the overall management of low-volume ovarian cancer, where it is most likely to be active.

NEW STUDIES

The GOG/Southwest Oncology Group (SWOG) has designed studies to evaluate Taxol in optimal stage III disease, to dissect the Taxol and cisplatin combination in

suboptimal disease, to definitively assess Taxol dose intensity in advanced platinum-resistant disease, and, finally, to evaluate Taxol doublets other than cisplatin/Taxol.

The phase III study in optimal stage III ovarian cancer had three arms: 1) intravenous cytoxan (750 mg/m^2) and cisplatin (75 mg/m^2), 2) intravenous Taxol (135 mg/m^2) and cisplatin (75 mg/m^2), and 3) high-dose intravenous carboplatin (to attain area under the curve = 9) for two cycles followed by intravenous Taxol (135 mg/m^2) and intraperitoneal cisplatin (100 mg/m^2). After data from the randomized study in suboptimal disease was noted, the first arm of this study was discontinued.

In suboptimal disease, a phase III study randomizes patients to the previous Taxol and cisplatin combination (135 mg/m^2 and 75 mg/m^2 , respectively), or to higher doses of each single agent (Taxol 200 mg/m^2 or cisplatin 100 mg/m^2). This study is important, too, because 15 years following the clinical development of cisplatin, we are still unsure of the relative roles of cytoxan and cisplatin in the current standard regimen. Although retrospective meta-analysis suggests that combinations with cisplatin are superior to cisplatin alone, no good prospective data confirm this (32).

Another phase III study randomizes patients with platinum-resistant ovarian cancer to one of three dose levels of Taxol (135 mg/m^2 , 175 mg/m^2 , and 250 mg/m^2) and to one of two doses of G-CSF ($5 \text{ } \mu\text{g/kg}$ or $10 \text{ } \mu\text{g/kg}$) for patients at the highest Taxol dose. This study will assess the effect of Taxol dose intensity on outcome and simultaneously compare the efficacy and toxicity of two different doses of G-CSF. Although previously cited phase II studies suggest a dose-response relationship, the low statistical power of those observations demands verification in a large phase III trial. The increased cost of high-dose Taxol combined with G-CSF as well as the emergence of sometimes disabling neurotoxicity demands a trial that evaluates more completely the therapeutic index of high-dose Taxol.

Finally, Taxol doublets with ifosfamide, etoposide, topotecan, carboplatin, and hexamethylmelamine will be evaluated in phase I trials. Ifosfamide, etoposide, and hexamethylmelamine have all been shown to have some activity in platinum-resistant ovarian cancer, and the combination of one or more of these agents with Taxol, if proven feasible, might contribute to improvement of salvage therapy. Topotecan is a topoisomerase I inhibitor that in phase I testing has shown some activity in refractory ovarian cancer (33,34). Lastly, study of the carboplatin doublet is important because carboplatin has less nephrotoxicity and neurotoxicity than cisplatin and equal efficacy in ovarian cancer when used in equivalent doses (32). Early results from this study suggest that nearly full doses of each agent can be combined with acceptable toxicity and a high degree of antitumor activity (35).

TAXOL: PRESENT ROLE AND FUTURE CLINICAL DEVELOPMENT

Taxol has already become the first-line salvage treat-

ment in platinum-resistant ovarian cancer. Skeptics may say that Taxol was never compared in a randomized study to other salvage therapies, but neither have any of the current salvage regimens been compared to each other. Data for single-agent Taxol are compelling: 157 responses among 626 evaluable patients, for an overall response rate of 25%, and response rates in platinum-resistant disease approach this figure (19-21,25,30). Response rates for other salvage therapies vary from 12% to 20% and have usually not been defined in platinum-resistant disease (15).

The routine inclusion of Taxol into primary therapy of suboptimal advanced ovarian cancer is likely based on early results of complete but immature phase III studies. Likewise, ongoing clinical trials should clarify the role of Taxol-based combination in earlier disease and whether dose intensification of Taxol improves outcome in ovarian cancer.

Intraperitoneal Taxol should be further evaluated as salvage therapy in patients with low-volume persistence or recurrence. We also believe there is a role for testing intraperitoneal Taxol in patients with high-risk, low-stage disease, currently treated with intraperitoneal ^{32}P . Similarly, intraperitoneal Taxol should be evaluated in patients with surgically confirmed CR after primary therapy. Trials in high-risk, low-stage disease and pathologic complete responders demand untreated controls to definitively evaluate this therapy.

The improvement in long-term survival of ovarian cancer has been modest, even after the introduction of cisplatin, and we share the concern of others about unrealistic expectations of Taxol in ovarian cancer (36). Nevertheless, we believe that early results of Taxol in initial therapy continue to suggest promise, and we encourage physicians to continue to enter patients in well-designed trials to better define this promise. The further unfolding of the Taxol story may well be another unfulfilled hope or, like cisplatin, another small step toward the cure of this disease.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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The M. D. Anderson Cancer Center Experience With Taxol in Metastatic Breast Cancer

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Taxol was evaluated in metastatic breast cancer in three trials. In the first, a phase II study, 25 patients who had received only one prior regimen of chemotherapy received Taxol (starting dose of 250 mg/m²). The response rates were 12% complete, 44% partial, and 32% minor. The median duration of response was 9 months (range, 3 to 19 months). The median survival was 20 months (range, 5 to 29+ months). Toxic effects were granulocytopenia less than 500/mm³ in 85% of all courses but serious infection in only 6% of courses, myalgias, and cumulative neuropathy. The second trial was a phase I study of Taxol by 24-hour infusion sequenced with doxorubicin by 48-hour infusion as initial chemotherapy for metastatic disease. In arm 1, Taxol preceded doxorubicin. The starting doses were 125 mg/m² Taxol, 60 mg/m² doxorubicin. Neupogen® (5 µg/kg) was given subcutaneously on days 5 through 19. Ten patients received 96 courses. The maximum tolerated dose was defined by mucositis and infection at the starting dose. Cumulative thrombocytopenia occurred in subsequent courses. The unexpectedly severe toxic effects at doses that were low by comparison to other studies suggested schedule-related toxicity. Therefore, in arm 2 the sequence has been reversed: doxorubicin precedes Taxol. Doses have been escalated to 180 mg/m² Taxol with 60 mg/m² doxorubicin without dose-limiting toxic effects occurring. The third trial, a phase II study in patients who have received three or more prior chemotherapy regimens, is ongoing. Twenty-one of a planned 35 patients have been entered. Taxol has shown significant antitumor activity in minimally pretreated patients. The combination of Taxol and doxorubicin is active, but the optimal doses and schedule are not known. The cardiac data suggest that outpatient treatment in an unmonitored setting is safe. [Monogr Natl Cancer Inst 15:161-169, 1993]

We have evaluated Taxol¹ in metastatic breast cancer in three trials. The first was a phase II study in patients who had received only one prior regimen of chemotherapy (1). The remaining studies are in progress. The second is a phase I trial of Taxol sequenced with doxorubicin as initial chemotherapy for metastatic disease (2), and the third is a phase II trial in patients refractory to three or more chemotherapy regimens.

TRIAL ONE: PHASE II STUDY IN PATIENTS WITH ONLY ONE PRIOR CHEMOTHERAPY REGIMEN

Patients and Methods

Eligibility. This study evaluated Taxol in patients with histologically diagnosed breast cancer and progressive and measurable or evaluable metastatic disease who had received only one prior regimen of chemotherapy (adjuvant to surgery or for metastatic disease). Eligibility criteria included Zubrod (3) performance status less than 3 [Karnofsky (4) scale greater than 70%], expected survival of at least 12 weeks, and adequate bone marrow, liver, and renal functions. All patients were advised of the investigational nature of this study, signed an informed consent document approved by the institutional human studies review board, and were registered with our central data management office.

Treatment details. Details of drug preparation and administration have been described previously (1). The drug was administered over 24 hours by continuous infusion every 21 days or when the patient had recovered from all toxic effects, whichever was later. All patients received standard premedication with 20 mg dexamethasone given orally 14 and 7 hours before Taxol treatment, and 300 mg cimetidine and 50 mg diphenhydramine given intravenously 1 hour before Taxol (5). The starting dose of Taxol was 250 mg/m². For patients with a high risk of severe myelosuppression (defined as prior irradiation to 30% of the marrow-bearing bones, prior treatment with mitomycin-C, or excessive myelosuppression requiring dose reduction in previous chemotherapy treatments) the starting dose was 200 mg/m². Subsequent dose reductions were 200, 180, 160, and 130 mg/m². Doses were reduced for grade 3 toxic effects or an absolute granulocyte count of less than 250/mm³. When clinical experience indicated that no excess of infectious or febrile episodes was associated with a granulocyte count of less than 250/mm³, doses were no longer reduced because of low absolute granulocyte counts alone. All treatment was given in an ambulatory treatment center. The planned duration of treatment was 12 months after a maximum response or 6 months for patients who had clinical benefit and no evidence of disease progression, unless toxic effects became intolerable.

Pretreatment evaluation. The pretreatment evaluation included a comprehensive history and physical examina-

*See "Notes" section following "References."

tion with attention to areas of clinical disease; laboratory evaluation including complete blood count with differential and platelet counts, serum chemistry, carcinoembryonic antigen assay (CEA); and appropriate radiographs and scans to document the extent of metastatic disease. During treatment, patients' vital signs were monitored twice during the premedication infusion, every 15 minutes twice after the initiation of the Taxol infusion, and then every 4 hours. No patients had any cardiac monitoring.

Between courses a complete blood count with differential and platelet counts was done twice weekly. Radiographs and scans were repeated after every two courses until response was documented and then after every three to four courses to confirm continuing response or to document progressive disease.

Assessment of response. We used the standard criteria for response determination (6). Briefly, complete remission required disappearance of all tumor for at least 4 weeks, with improvement of bone lesions by bone scan, complete normalization of bony architecture by x ray, normalization of CEA, and no symptoms of cancer. A partial response was a 50% or greater decrease in the sum of the products of perpendicular diameters of all measured lesions and the appearance of no new lesions. Evaluable lesions such as those in bones must have evinced improvement on bone scan and blastic response on x rays. CEA must have decreased, and all responses must have persisted for a minimum of 4 weeks. Minor response was a less than 50% decrease in the size of any measurable lesions or a response that lasted less than 4 weeks. No change indicated no evidence of change in tumor size or less than a 25% increase in tumor size for at least 4 weeks. Progressive disease was the appearance of any unequivocally new lesions or an increase of 25% or more in the sum of the products of the perpendicular diameters of measured lesions or in the estimated size of any non-measurable lesions.

Results

From January through August 1990, 25 patients were entered on the trial. Response and survival results have been updated as of September 1992. Patient characteristics are shown in Table 1. Most patients had visceral disease, and three quarters had bidimensionally measurable disease.

Overall responses as well as responses by prior therapy are shown in Table 2. The overall response rate was 56% [95% confidence interval (CI)=35%-76%], 12% complete remissions, 44% partial remissions, and 32% minor responses. Three of the eight patients with minor responses had unusually long responses (7.6, 9.9, and 14.4 months). The median duration of response was 9 months (range, 3-19 months). The median time to disease progression was 9 months (range, 1-20 months). The median overall survival was 23 months (range, 5-29+ months). The median number of courses per patient was 13 (range, 2-21 courses). All but two patients received more than two courses. The only patients with initial failure to Taxol had received therapy for metastatic disease.

Table 1. Patient characteristics for phase II trial (one prior chemotherapy regimen)

Characteristics	Result	Range
Number entered	25	
Number evaluable	25	
Median age, y	51	34-70
Median Zubrod performance status	1	0-2
Median disease-free interval, mo	18	0-94
Estrogen receptor (ER) status, number of patients		
Negative	9	
Positive	14	
Unknown	2	
Median ER value, fm/mg, of ER positive	25.5	10-433
Prior hormone therapy	15	
Prior chemotherapy	25	
Adjuvant	14	
Metastatic	11	
Prior doxorubicin	23	
Doxorubicin-resistant*	6	
Dominant disease site		
Soft tissue	6	
Bone	4	
Visceral	15	
Median number of sites	2	1-10
Median number of organs involved	2	1-6

*Doxorubicin resistance is defined in the text in the "Results" section.

Twenty-three patients had received doxorubicin previously, either as adjuvant therapy (12 patients) or for metastatic disease (11 patients). Patients who relapsed after an initial response to doxorubicin were considered secondarily resistant. Patients whose tumors had progressed during doxorubicin de novo or who relapsed within 6 months of an adjuvant regimen were considered to have primary doxorubicin resistance. Six patients were doxorubicin resistant. One patient relapsed at completion of adjuvant therapy. Five patients relapsed after an initial response to a doxorubicin-based regimen for metastatic disease. One patient relapsed 3 months after completing 10 months of a doxorubicin-based regimen that induced a partial response. Of these six patients with doxorubicin resistance, two had partial responses lasting 6.1 and 2.5 months; two had minor responses lasting 2.3 and 2.8 months; and in two patients, tumors continued to progress without any intervening response.

Hematologic toxicity. All treatments were completed by August 1991; 297 courses were administered. Toxic effects are summarized in Table 3 by patients and by courses. The

Table 2. Responses—overall and by prior chemotherapy

Response	Total, N=25	Adjuvant, N=14	Metastatic, N=11
Complete	3	2	1
Partial	11	6	5
Minor	8	6	2
No change	1	0	1
Progression	2	0	2

Table 3. Incidence of grades 2 and 3 toxic effects by patients and courses

Toxic effect	By patient, % N = 25	By courses, % N = 232
Neutropenia less than 500/mm ³	100	85.8
Infection	8	0.9
Fever during neutropenia*	36	4.7
Diarrhea		
Grade 2	60	13.8
Grade 3	4	0.4
Stomatitis-2	32	6.0
Myalgia/arthralgia		
Grade 3	16	3.0
Neuropathy		
Grade 2	52	15.1
Grade 3	8	0.9

*Neutropenia = less than 1000 granulocytes/mm³.

dose-limiting toxic effect was neutropenia in all but four patients who had dose reductions because of grade 3 myalgias; seven patients required no dose reductions. Seven patients initially received the lower 200 mg/m² dose because they were at high risk for myelosuppression. The median dose was 200 mg/m².

Myelosuppression was profound, though not cumulative, and platelets and red blood cells were spared (1). The median lowest recorded granulocyte count was consistently 100 to 200/mm³. The range for all dose levels always included 0/mm³. The median granulocyte nadir occurred on day 8 (range, 7–25 days) in the initial course but was prolonged to day 12 (range, 8–17 days) in subsequent courses. Despite this, infection or fever during neutropenia occurred in only 6% of courses (Table 3).

Nonhematologic toxic effects. The syndrome of myalgias and arthralgias, similar to the prodrome of influenza and seen in patients treated with high doses of vinblastine, was observed in most patients. This began 3 to 6 days after treatment and lasted 3 to 6 days. Commonly, the lower extremities, pelvis, and lower back were affected, but the upper extremities were involved in some patients. While the intensity of this reaction varied among patients, in each patient it was directly related to the Taxol dose. Symptomatic treatment with nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, and standard morphine-based analgesics proved helpful in all but four patients in whom the symptoms were severe enough to necessitate dose reduction.

Cardiac toxicity. Only four cardiac events occurred during this study. Two patients developed sinus bradycardia during the infusion. One of these was known to have a preexisting sinus bradycardia, but the other patient had no underlying history of sinus rhythm disturbance and was completely asymptomatic. A third patient had an episode of sinus pause, one lasting longer than 2 seconds in course number 10. No further episodes occurred despite Holter monitoring before and during three subsequent courses. The fourth patient, who had mitral valve prolapse with atypical chest pain, experienced atypical chest pain with ventricular ectopy 3 days after the second course. Evalua-

tion revealed no evidence of myocardial infarction, and no new abnormalities were noted on echocardiogram. The patient had progressive disease and discontinued further therapy.

Neurologic toxic effects. Some patients experienced an acute neuropathy manifested by tingling of the fingertips and toes that began within 24 hours of the infusion. This often merged into the myalgia syndrome. Most patients developed a cumulative and chronic glove-and-stocking sensory neuropathy that was associated with complete loss of deep tendon reflexes. In some patients this was painful and associated with hyperalgesia. Some patients complained of diminished fine motor skills (for example, buttoning or fastening clasps on jewelry). When doses were reduced, these symptoms did not progress. After completion of therapy, these symptoms improved.

Other toxic effects. In addition to universal alopecia totalis, a visible and commonly experienced side effect was the well-described cutaneous reaction to high doses of dexamethasone, an erythroderma over the sun-exposed areas of the face, chest, and upper torso. It progressed to a fine scale and resolved over 2 to 3 days.

TRIAL TWO: PHASE I TRIAL OF SEQUENTIAL ADMINISTRATION OF TAXOL AND DOXORUBICIN AS INITIAL THERAPY FOR METASTATIC BREAST CANCER

The high response rates and the long duration of the responses seen in the previous study suggested that Taxol was extremely active in breast cancer. The next logical step was to combine it with the known most active drug, doxorubicin. In view of the potential overlap between the severe myelosuppression seen with Taxol and doxorubicin's known myelosuppressive effects, colony-stimulating factors were added to the regimen to abrogate myelosuppression. To properly evaluate the activity of this combination, it was used as the initial therapy for patients with metastatic disease. The objective was to determine the maximum tolerated doses (MTD) of Taxol in sequential combination with doxorubicin.

Patients and Methods

Eligibility. Eligible patients were those with a histologically diagnosed, measurable, or evaluable metastatic breast cancer for which no chemotherapy had been given. Patients may or may not have received adjuvant therapy. If adjuvant therapy had been administered, it must not have included doxorubicin unless relapse occurred more than 6 months after completion of doxorubicin. To ensure that patients have adequate cardiac reserve to tolerate further doxorubicin, those patients who had received doxorubicin must have received less than 300 mg/m² by short intravenous infusion or less than 400 mg/m² by continuous infusion. Isotope cardiac scans with determination of left ventricular ejection fraction (LVEF) must be monitored at The University of Texas M. D. Anderson Cancer Center, and the LVEF must be greater than 60%.

All other eligibility criteria described for trial one apply, including signing an informed consent document.

Treatment details. Taxol was administered over 24 hours followed immediately by doxorubicin over 48 hours; treatments were repeated every 21 days or as soon as the patient had recovered from all toxic effects, whichever was later. Standard premedication (5) was administered as for trial one. The starting dose level was 125 mg/m² Taxol and 60 mg/m² doxorubicin. Granulocyte-colony stimulating factor Neupogen® (Amgen Pharmaceuticals, Thousand Oaks, Calif.) was supplied by the National Cancer Institute and administered at a dose of 5 µg/kg daily on days 5 through 19. Table 4 shows the projected dose escalation schema as well as the actual de-escalation schema used. The standard phase I dose escalation process was used: three patients were treated at each dose level and, if at any of the dose levels none of the patients developed grade 3 or higher toxic effects (excluding grade 3 granulocytopenia), the next three patients were treated at the next higher dose level. In view of the lack of serious toxic effects associated with the brief though profound granulocytopenia in the previous study, dose-limiting granulocytopenia was defined as an absolute granulocyte count of less than 500/mm³ associated with fever or infection or an absolute granulocyte count of less than 250/mm³ for more than 5 days. If any of three patients developed any of these symptoms, three additional patients were to be treated at the same dose level. If any three patients developed grade 3 toxic effects or dose-limiting granulocytopenia or any two patients developed grade 4 toxicity, that dose was defined as exceeding the MTD. The MTD would be one dose below the dose at which two to three of six patients who were started at a given dose level developed grade 3 toxic effects or dose-limiting granulocytopenia. Dose escalation was not permitted for individual patients. All treatment was to be continued for six courses after achieving maximum response or for a maximum of six courses unless there was definite evidence of progressive disease or intolerable toxic effects.

Evaluation before and during treatment. Pretreatment evaluation was identical to that described for trial one with the addition of baseline isotope cardiac scan with determination of LVEF, 24-hour Holter monitor, and evaluation by a cardiologist. Evaluation during the study included the same laboratory parameters except daily or every other day granulocyte counts during the expected period of granulocytes less than 500/mm³. Toxic effects were graded according to the National Cancer Institute's common toxicity criteria (7).

Initially, all patients had real-time as well as 72-hour Holter monitoring during the entire infusion of chemotherapy. When subsequent evaluation (8) revealed no problems, two changes were made: first, after the initial three courses the real-time cardiac monitors were eliminated; second, treatment was administered in an ambulatory setting with portable pumps, and patients were monitored with 24-hour Holter monitors only during the infusion of Taxol.

Table 4. Dose escalation and reduction schedule for phase I trial of Taxol with doxorubicin

Dose level	Taxol, mg/m ²	Doxorubicin, mg/m ²
3	180	60
2	150	60
1	125	60
-1	125	48
-2	100	48
-3	100	40
-4	90	36
-5	80	30

LVEF was determined for each patient after every two courses of therapy. If the LVEF was below 60%, an endomyocardial biopsy was performed and scored with a modified Billingham scale (9). An endomyocardial biopsy score of 1.0 or less was adequate for continued treatment with doxorubicin. For patients in whom further doxorubicin was considered unsafe, Taxol was given as a single agent at the highest tolerable dose (160 to 200 mg/m²). Responses were assessed as described above.

Results

Patient characteristics and responses. From August 1991 to July 1992, 10 patients received 106 courses on the Taxol-doxorubicin sequence. Results are updated as of September 1992. Patient characteristics are shown in Table 5. Again, the dominant site of disease is visceral.

Eight patients had an objective response (95% CI = 44%–98%), of which one was a complete response. One patient had a minor response, and one patient had no change. The median duration of response was 6 months (range, 3–8 months). The median time to progression was 9 months (range, 4–10 months). The median overall survival has not yet been reached at greater than 10 months (range, 9–13+ months).

Maximum tolerated dose. At dose level 1, three of six patients experienced dose-limiting toxic effects: stomatitis, neutropenic fever, or both. Thus, for those patients and for the second cohort of three patients, doses were reduced to the -1 level: 125 mg/m² Taxol and 48 mg/m²

Table 5. Patient characteristics for phase I trial, arm 1: Taxol preceding doxorubicin

Characteristics	Result	Range
Number entered	10	
Number evaluable	10	
Median age, y	48	36–62
Median Zubrod performance status	1	0–2
Median disease-free interval (months)	20	0–72
Prior adjuvant therapy	6	
Prior doxorubicin	3	
Dominant disease site		
Soft tissue	1	
Bone	1	
Visceral	8	
Median number of sites	2	1–9

doxorubicin. No patient experienced grade 3 toxic effects at this dose level. Thus, the MTD for the schedule was defined as 125 mg/m² Taxol and 48 mg/m² doxorubicin. Two of the three patients who did not experience dose-limiting toxicity in course one required dose reduction in course three. Only one patient was able to continue for six courses at the initial starting dose. Overall, doses in 22% of courses were reduced. The reasons for dose reduction were stomatitis, fever with neutropenia, thrombocytopenia, or a combination. No patient received escalated doses.

Hematologic toxic effects. Hematologic toxic effects are shown by course in Table 6, for courses 1, 2, 3, 6, and 10. Despite the use of granulocyte-colony stimulating factor, the lowest recorded granulocyte count remained low until later courses when most patients received reduced doses. More important, however, as shown in Table 6, was the evidence of progressive thrombocytopenia. This is uncommon with the standard initial combination chemotherapy regimen of 5-fluorouracil, cyclophosphamide, and doxorubicin (FAC). However, no patient required platelet transfusions because doses were reduced in subsequent courses. Additionally, the time course of occurrence of myelosuppression and thrombocytopenia was reversed. With standard FAC, the platelet count usually decreases first and the granulocytes second. This phenomenon may reflect the effects of granulocyte-colony stimulating factor.

Other toxic effects. Nonhematologic grade 2 and 3 toxicities are listed by patients and by courses (Table 7). All patients experienced grade 2 or 3 stomatitis at some time during therapy, although in most patients it was grade 2. Despite dose modification in subsequent courses, stomatitis continued to occur. In contrast, although most patients experienced infection or fever, subsequent dose modification reduced the frequency of these effects in later courses. All patients had total alopecia. The toxic effects not listed here were generally mild. There were no allergic reactions and no serious cardiac events requiring therapy. Only one patient developed the well-described myalgia syndrome, curiously, after course number four, in which doses were relatively low (100 mg/m² Taxol and 48 mg/m² doxorubicin).

One unusual cardiac event occurred of unclear significance. One patient had an increased incidence of premature ventricular contractions, from 2.4 per hour to 164 and 128 per hour during treatment with Taxol and doxorubicin, respectively. These were not symptomatic, were not treated, had no clinical sequelae, and never recurred during subsequent courses.

Schedule-dependent toxic effects? The MTD for this sequential combination of Taxol and doxorubicin was defined by stomatitis and infection at doses much lower than anticipated. A similar trial reported by Fisherman et al. (10) used 72-hour concurrent administration of Taxol and doxorubicin and administered higher doses of both drugs without unacceptable toxic effects. We hypothesized that an interaction between Taxol and doxorubicin was producing schedule-dependent toxicity such as that reported for Taxol and cisplatin by Rowinsky et al. (11). This led us to test the reverse schedule of Taxol and doxorubicin and to evaluate pharmacokinetics.

In arm 2, doxorubicin was administered over 48 hours on days 1 and 2, followed by Taxol over 24 hours on day 3. The starting dose was the MTD determined in the first arm, namely doxorubicin, 48 mg/m², and Taxol, 125 mg/m². All other monitoring and evaluations were identical.

Patient characteristics are shown in Table 8. No patient experienced dose-limiting toxic effects in the reverse schedule, so dose escalation began. We are completing accrual at level +3, with 180 mg/m² Taxol and 60 mg/m² doxorubicin. Sixteen patients have received 103 courses. The study is ongoing, and it is too early for an assessment of full response rates. However, initial evaluation reveals four patients have partial responses, six have minor responses, one is unchanged, and five patients are too early for evaluation. Hematologic toxic effects are shown in Table 9.

After the MTD for the reverse sequence is determined, six additional patients will be treated, and the pharmacokinetics will be performed to evaluate whether Taxol affects doxorubicin clearance. Three patients will receive the sequence of Taxol followed by doxorubicin for course one, and three others will receive the reverse sequence. In course two, each group of patients will receive the opposite schedule, thus serving as their own controls. After the initial two courses, all patients will be treated with the

Table 6. Hematologic toxic effects by course, phase I trial, arm 1: Taxol preceding doxorubicin

Course	1	2	3	6	10
No. of patients	10	10	10	9	2
Median dose Taxol/doxorubicin, mg/m ²	125/60	125/48	125/48	125/48	125/48
Median lowest recorded AGC*/mm ³ , × 10 ³	0.13	0.52	1.04	1.16	0.85
Range	0-6.2	0.02-7.48	0.03-5.56	0.54-3.08	0.35-1.35
Median no. days AGC less than 250/mm ³	3	2.5	2	0	0
Median day lowest AGC	9	9	10	10.5	7
Range	8-11	4-11	5-11	5-11	4-10
Median lowest recorded platelets/mm ³ , × 10 ³	127	88	53	54	103
Range	34-217	35-217	19-222	25-151	95-109
Median day lowest platelets	12	11	11	11	11
Range	8-15	9-14	10-12	9-12	10-12

*Absolute granulocyte count

Table 7. Nonhematologic grades 2 and 3 toxic effects by patients and by courses for phase I trial, arm 1: Taxol preceding doxorubicin

	% Patients, N = 10	% Courses, n = 77
Stomatitis	100	60
Infection/fever	80	16
Vomiting	40	20
Nausea	40	14
Alopecia	100	100

sequence of doxorubicin followed by Taxol at the highest tolerable dose. Additional pharmacokinetic studies at this level will evaluate whether the pharmacodynamics are linear at higher doses. Lastly, in arm 4, the MTD will be determined for the combination with doxorubicin administered first by a short intravenous infusion (instead of a 48-hour infusion).

TRIAL THREE: PHASE II STUDY IN PATIENTS WHO HAVE RECEIVED THREE OR MORE PREVIOUS CHEMOTHERAPY REGIMENS

The activity of Taxol in patients with ovarian cancer who had become refractory to platinum-based therapies (12) suggested that Taxol may have significant activity in patients with breast carcinoma who had become refractory to standard therapy. Furthermore, two of six patients in trial one who had shown doxorubicin resistance did respond to Taxol. For this reason, a trial of Taxol in patients with metastatic breast cancer refractory to doxorubicin and whose tumors have progressed after three or more prior chemotherapy regimens was planned. Although myelosuppression is known to be the dose-limiting toxic effect, the ovarian cancer studies and trial one did not demonstrate a clear dose-response relationship. This trial, which is ongoing, was designed, therefore, to evaluate the efficacy of Taxol without colony-stimulating factors. Moreover, since this treatment is palliative, it is important to consider its effects on the quality of life (13). The study's second objective is to monitor concurrently patients' quality of life while receiving this treatment.

Table 8. Patient characteristics for phase I trial, arm 2: doxorubicin preceding Taxol

Characteristics	Result	Range
Number entered	16	
Number evaluable	16	
Median age, y	46	32-66
Median Zubrod performance status	0	0-2
Median disease-free interval, mo	14	0-41
Prior adjuvant therapy	12	
Prior doxorubicin	3	
Dominant disease site		
Soft tissue	-	
Bone	1	
Visceral	15	
Median number of sites	2	1-4

Patients and Methods

Eligibility. Eligible patients are those with metastatic breast carcinoma resistant to three or more standard chemotherapy regimens. Patients must have adequate bone marrow reserve defined as a granulocyte count of $1500/\text{mm}^3$ or higher, a platelet count of $100\,000/\text{mm}^3$ or higher, and irradiation to no more than 25% of the marrow-bearing bones. Patients may have had brain metastases, but these must be controlled without steroids for at least 6 months. Because of the requirement that a quality-of-life questionnaire be completed before each course, all patients are required to speak and read English. Other eligibility criteria are the same as for trial one.

Treatment details. Taxol is administered over 24 hours every 21 days or as soon as the patient has recovered from all toxic effects, whichever is later. The starting dose is $150\text{ mg}/\text{m}^2$. Patients who have received mitomycin-C or irradiation up to 25% of the bone marrow are considered at high risk for myelosuppression; the starting dose for these patients is $135\text{ mg}/\text{m}^2$. Standard premedication is used, as described previously (5). All patients are treated in the ambulatory treatment center with monitoring of vital signs but no cardiac monitoring. The planned duration of therapy is for six courses after maximum response, or for at least three courses if the tumor is unchanged and the patient does not experience intolerable toxic effects, or for two courses if the patient develops unequivocal evidence

Table 9. Hematologic toxic effects by course, phase I trial, arm 2: doxorubicin preceding Taxol

Course	1	2	3	6	9
No. of patients	16	15	14	10	4
Median dose, mg/m^2 Taxol/doxorubicin	125/60	125/60	125/48	125/48	125/48
Median lowest recorded AGC [*] / mm^3 , $\times 10^3$	0.1	0.6	1.4	2.1	4.7
Range	0-1.0	0.1-12.5	0.0-1.8	0.0-5.1	1.1-15.1
Median day lowest AGC	9.5	10	11	10.5	12.5
Range	9-11	2-12	1-12	2-27	9-26
Median lowest recorded platelets/ mm^3 , $\times 10^3$	118	111	67	78	98
Range	44-174	54-201	28-168	24-274	84-132
Median day lowest platelets	9	12	11	10.5	12.5
Range	9-17	2-17	9-14	2-20	12-15

*Absolute granulocyte count.

of progressive disease. For patients whose disease was clearly progressing before receiving Taxol and who experience no change in disease after receiving Taxol, treatment is continued to a maximum of six courses.

Evaluation before and during study. Pretreatment evaluation includes the standard evaluation described previously, with a baseline electrocardiogram, 24-hour Holter monitor, and determination of isotope cardiac LVEF. All patients complete a Quality of Life Measurement-Breast Cancer (14).

Evaluation between courses will consist of weekly complete blood counts with differential and platelet counts. The hemogram is repeated every other day or daily as necessary to define hematologic toxic effects and if the platelet count is less than 50 000/mm³. The Quality of Life Measurement-Breast Cancer must be completed before each treatment in courses one through six, then every three courses, and at the time the patient discontinues treatment.

Results

Patient characteristics. As of January 1993, 21 patients have been entered since June 1992. The characteristics are shown in Table 10. All patients have had significant amounts of prior chemotherapy. In two patients, high dose regimens were used.

Responses. Preliminary results in 18 patients evaluable for response are 33% partial, 11% minor, and 28% no change. Five patients (28%) have progressed during the initial two treatments, and one of these patients has expired.

Toxic effects. Hematologic toxic effects for the first 12 patients are shown by course in Table 11. Nonhematologic toxicity has included stomatitis, neutropenic fever, and myalgias. The one patient who died was unusual in having a history of beta thalassemia and low-grade hemolysis. She experienced a syndrome of increased hemolysis with altered mental status, but neither renal function nor platelet counts were altered to make definitive diagnosis of a hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. She had acute respiratory distress that was

Table 11. Hematologic toxic effects

Course	1	2
No. of patients	12	7
Median dose Taxol, mg/m ²	150	150
Median lowest recorded AGC*/mm ³ , × 10 ³	0.0	0.2
Range	0-1.5	0.0-1.0
Median day lowest AGC	10	11.5
Range	7-14	8-14
Median lowest recorded platelets/mm ³ , × 10 ³	131	136
Range	55-249	82-264
Median day lowest platelets	8	8
Range	4-10	2-11

*Absolute granulocyte count.

later shown to be rapid progression of lymphangitic lung metastases. The patient was treated with plasma exchange and high-dose steroids. Her hemolytic process reversed, but she continued to develop rapidly progressive disease in soft tissue and lung.

DISCUSSION

Our initial study showed that Taxol is an active agent in breast cancer in patients who received one prior treatment. Its single-agent activity was comparable to standard first-line combination regimens, and the duration of response was substantial. However, the sample size was necessarily limited by drug supply problems, and the confidence intervals are wide. One other study (15,16) confirmed the activity of Taxol in this population. That study was somewhat compromised by even more limited availability of the drug, necessitating early discontinuation of therapy. Interestingly, doses were reduced in a majority of patients despite the use of colony-stimulating factors. Higher doses of colony-stimulating factors may abrogate problems with myelosuppression and fever, but neurotoxic effects and mucositis may become dose limiting with higher doses of Taxol.

Our second study has tantalized us with the possibility that there is a drug-drug interaction between Taxol and doxorubicin, similar to that between Taxol and cisplatin described earlier by Rowinsky et al. (11). Patients in another study using concurrent administration of Taxol and doxorubicin for 72 hours experienced less stomatitis than has been seen in our study. Because longer durations of doxorubicin infusion are usually associated with increased probability of mucositis, one possible explanation is that Taxol somehow blocks the expected doxorubicin-induced mucositis. We anticipate that our pharmacologic studies will evaluate whether this effect was dependent on the sequence of drug administration.

Of particular concern is the severity of the thrombocytopenia seen in some patients who received the combination of doxorubicin and Taxol. Admittedly, the use of colony-stimulating factors allows higher doses of both

Table 10. Patient characteristics for phase II trial, refractory metastatic breast cancer

Characteristics	Result	Range
Number entered	21	
Number evaluable	18	
Median age, y	52	39-75
Median Zubrod performance status	1	0-2
Median disease-free interval, mo	25	0-107
Median number prior chemotherapy regimens	4	3-7
Prior doxorubicin	18	
Dominant disease site		
Soft tissue	3	
Bone	0	
Visceral	18	
Median number of sites	4	1-8

drugs, but this thrombocytopenia is in excess of that seen with standard FAC therapy. The enhanced and cumulative thrombocytopenia produced by this combination and schedule may indicate that this combination and schedule are not optimal.

Although response rates were high in this second study, the sample size is small and confidence limits are wide (95% CI = 44–98). These patients have been very highly selected and have had extensive disease. The durations of response have not been exceptionally long. It is too early to comment on the durability of responses in the second arm of the study. However, the toxic effects in this arm are much milder, and doses are escalating. Pharmacologic studies should conclusively demonstrate the nature of any drug-drug interaction.

The use of Taxol as a fourth or later salvage regimen for patients with metastatic disease is now being studied.

Recent work by Huber et al. (17) at our institute suggests that duration of exposure may be crucial to the activity of this drug, as is true for vinblastine (18). Future studies will address appropriate drug combinations and the importance of schedule.

ADDENDUM

Since submission of this manuscript, the reverse schedule in trial two (phase I trial of sequential administration of Taxol and doxorubicin, in which doxorubicin preceded Taxol) has been completed. The MTD was 60 mg/m² doxorubicin with 150 mg/m² Taxol. The dose-limiting toxic effect was neutropenia. Preliminary results from the subsequent pharmacology studies suggest that, when Taxol precedes doxorubicin, the maximum doxorubicin concentration and the doxorubicin area under the curve are increased. This correlates with the increased stomatitis seen with the initial schedule at lower doses.

Also, in trial three (phase II study in patients who have received three or more previous chemotherapy regimens), the response rate in 32 evaluable patients is 19%.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Taxol Plus Recombinant Human Granulocyte-Colony Stimulating Factor as Initial and as Salvage Chemotherapy for Metastatic Breast Cancer: A Preliminary Report

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Twenty-eight patients received Taxol as their first chemotherapy for stage IV breast cancer. An additional 51 patients with extensive prior exposure to other chemotherapeutic agents received Taxol as salvage therapy. We found significant activity for the drug in both situations, as well as a strong clinical suggestion of non-cross-resistance with doxorubicin. An excellent response in previously irradiated skin was noted in one case. The routine use of recombinant human granulocyte-colony stimulating factor seemed to ameliorate some of the dose-limiting toxicity of neutropenia. Other toxicity was mild to moderate in most cases. With further development, Taxol should play a significant role in the systemic management of breast cancer. [Monogr Natl Cancer Inst 15:171-175, 1993]

Taxol,¹ a diterpene derived from the bark of *Taxus brevifolia*, promotes the formation of tubulin dimers and inhibits the depolymerization of microtubules, resulting in an antineoplastic effect (1-4). Based on xenograft data (5) and on a prior report of significant activity of Taxol in the treatment of metastatic breast cancer (6), we studied the drug as initial chemotherapy and as salvage chemotherapy for stage IV disease. In an attempt to ameliorate myelosuppression, which had been dose limiting in previous trials, and which was observed in the first two patients we treated with Taxol, recombinant human granulocyte-colony stimulating factor (rhG-CSF) was used routinely in all subsequent cases.

MATERIALS AND METHODS FOR TAXOL AS INITIAL THERAPY

Eligibility criteria for our study of Taxol as first chemotherapy included histologic evidence of breast cancer; documentation of stage IV disease; no prior chemotherapy for metastatic disease; 12 or more months of elapsed time after cessation of postoperative adjuvant chemotherapy (if any); no more than one prior hormone therapy in the adjuvant setting and/or as treatment for metastatic disease; measurable, nonirradiated lesion(s); radiotherapy greater than or equal to 4 weeks previously and to no more

than 30% of the bone marrow; absence of untreated central nervous system disease; no lymphangitic lung metastases or carcinomatous meningitis; adequate renal and liver function; no hypercalcemia; and no other serious medical, surgical, or psychiatric condition. Full informed consent was obtained from the patients in all cases.

Between April and October 1991, we accrued 28 patients to study. Their median age was 52 years (range, 30-67 years), and their median Karnofsky performance status was 90% (range, 70%-100%). The pre-Taxol disease was extensive in most of the patients: 82% had two or more organ-system sites of metastases; 39% had three or more. Prior postoperative adjuvant therapy had been used in 61% at a median disease-free interval off-treatment of 20 months (range, 12-47). Half of the prior adjuvant therapies had contained doxorubicin. Two patients had received vincristine in the adjuvant setting. Eleven patients had received prior hormone therapy: five as adjuvant, two for stage IV disease, four for both.

Based on prior phase I experience (7,8), the starting dose of Taxol was 250 mg/m² administered as a continuous 24-hour intravenous (IV) infusion every 21 days. Supplied by the National Cancer Institute in polyoxyethylated castor oil in ethanol (Cremophor EL[®]), the drug was diluted to 0.3-1.2 mg/mL in 5% dextrose or 0.9% saline solutions. In-line filters (0.2 μ m, IVEX-2, Abbott), glass containers, and polyethylene-lined nitroglycerine tubing were used. Dosage escalations and reductions were planned on the basis of toxicity; to maintain consistency with the prior clinical trial methodology for dose modification used in the initial M. D. Anderson study, the presence of a single absolute neutrophil count of less than 250 cells/mm³ was used as a criterion for dose reduction by one level—patients with febrile neutropenia were reduced two dose levels. Duration of neutropenia was not a criterion for dose reduction per se, unless treatment was unable to be recycled within 35 days because of prolonged myelosuppression. For all but the first two patients, rhG-CSF (Amgen) was given daily at 5 μ g/kg/day subcutaneously on days 3-10.

The administration of drugs in Cremophor EL has been associated with a hypersensitivity reaction that is probably due to histamine release rather than true allergy (9). The reaction is often seen on first exposure and may not recur on rechallenge with subsequent courses of treatment. To

*See "Notes" section following "References."

prevent this complication, patients in our trials received the well-established regimen of 20 mg dexamethasone given orally at hours -14 and -7, and 300 mg cimetidine and 50 mg diphenhydramine hydrochloride IV at hour -1 prior to the Taxol infusion over hours 0-24 (4,10-12). Steady-state drug levels were obtained to determine if response and/or toxicity correlated with plasma levels of the parent compound. To conserve drug, treatment was planned to be terminated after two cycles beyond best response or 10 cycles if the disease was stable.

Initial evaluation and assessment of response were by history; physical examination; complete blood count; biochemical tests of renal and liver function, lactate dehydrogenase, uric acid, serum calcium and phosphorous, carcinoembryonic antigen, and CA 15-3; electrocardiogram; chest radiograph; and radiological imaging of index lesions as indicated. The β -human chorionic gonadotropin test was used to screen premenopausal women for pregnancy.

RESULTS OF TAXOL AS INITIAL THERAPY

In the first cycle of administration, more than half of the patients experienced a neutrophil nadir less than 500 cells/mm³. The first two patients did not receive rhG-CSF. They experienced severe neutropenic nadirs (below 200 cells/mm³) at 2 weeks and required an additional 2 weeks for full recovery. Administration of rhG-CSF for all subsequent patients was associated with a median of just 2 days of such neutropenia, the nadir occurring at about 1 week after treatment. One patient's granulocyte nadir was sufficiently high that her dose of Taxol was escalated to 300 mg/m². Just under half of the patients required dose reductions in the second cycle. Of the 27 patients who received more than one course, 30% were able to receive subsequent therapy without dose reduction. The median dose of Taxol in the third and subsequent cycles was 200 mg/m². Only one patient developed significant thrombocytopenia. Treatment was never delayed because of slow hematological recovery when G-CSF was used. Although treatment was well tolerated, adverse effects included generalized alopecia in all patients and, in most patients, mild myalgias, arthralgias, and peripheral neuropathy (less than grade 2). Only one patient developed grade 3 nausea, but she was found to have an expanding pericardial effusion, the surgical treatment of which eliminated her nausea in subsequent cycles. Prior exposure to vincristine did not predispose to Taxol neuropathy in our small experience. Eight of 178 cycles of treatment resulted in admission for neutropenic fever. Twenty-two patients (79%) did not require admission for neutropenic fever. One patient with severe liver disease was hospitalized for mucositis and dehydration (plus pancytopenia and fever). This patient had a peak Taxol level in plasma that was significantly higher than the median for all patients of approximately 1 μ M. The median number of courses administered per patient was six (range 1-15). No hypersensitivity reactions and no hemodynamic instability nor cardiac toxicities were observed.

Two patients were not evaluable for response, in one case because the patient had received two prior hormone therapies for stage IV disease (this patient had stable disease after four cycles of Taxol) and in the other case because of an unrelated automobile accident. Objective responses by standard criteria (13) were observed in 16 of the 26 evaluable patients (62%; 95% confidence interval, 41-80). There were three (12%) complete responses (lymphadenopathy and pleural effusion, lymphadenopathy, and lymphadenopathy and skin in a site that had previously received radiotherapy) and 13 (50%) partial responses seen in visceral, osseous, cutaneous, and nodal sites. Bone responses were associated with marked relief of pain. Ten of 16 patients (63%) who had received prior adjuvant chemotherapy responded. This included one complete and four partial responses among eight patients who had received prior doxorubicin-containing adjuvant therapy. Eight patients had received CMF variants (cyclophosphamide-methotrexate-5-fluorouracil) as adjuvant treatment: Of these, two experienced complete remission from Taxol, and three entered partial remission. The median time to first objective response was 5 weeks (range, 1-14), and the median time to best response was 6 weeks (range, 1-14). Hormone receptor status or prior hormone therapy did not seem to influence the probability of response.

MATERIALS AND METHODS FOR TAXOL AS SALVAGE THERAPY

To study the activity of Taxol against tumors with extensive prior exposure to chemotherapeutic agents, we conducted a trial that was open only to patients whose disease had proved refractory to at least two prior regimens administered in the setting of metastatic disease, one of which had to contain an anthracycline or anthracenedione. Between February and April of 1992, we accrued 51 such patients to trial. They had received a median of three prior chemotherapy regimens, with a range of two to six. The median age was 47 years (range, 29-73 years), and the median Karnofsky performance status was 70% (range, 60%-90%). Thirty-four patients (67%) had received prior radiation therapy for stage IV disease. Seven patients (14%) had received prior high-dose chemotherapy of the "autologous bone marrow transplantation" type (e.g., at sufficiently myelotoxic doses to require rescue by reinfusion of autologous bone marrow or peripheral blood progenitor cells with hematopoietic growth factors). Twenty-two patients had breast cancer with demonstrated primary resistance to doxorubicin or mitoxantrone; 27 had previously responded transiently to doxorubicin or mitoxantrone but then had had disease progression; two had had stable disease (one on each agent). Sites of metastases included bone in 47% of patients, lymph nodes in 43%, liver in 33%, skin or soft tissue in 47%, and lung or pleura in 45%. The median number of metastatic sites was three (range, 1-7), and 86% of patients had more than one involved site.

As we anticipated more pronounced toxicity in this heavily treated patient population than in the prior group, a lower starting dose of Taxol, 200 mg/m², was chosen, with the opportunity for dose escalation in the absence of significant observed toxicity. In contrast to our trial in patients receiving Taxol as initial chemotherapy for metastatic disease, we chose to use the *event* of febrile neutropenia rather than a predetermined degree and/or duration of neutropenia as a criterion for dose reduction. Taxol administration typically results in deep neutropenic nadirs; however, with concurrent administration of G-CSF, the duration of these nadirs in our first trial was brief—shorter than the published prior experience, where patients receiving Taxol as a second chemotherapy regimen at 200 to 250 mg/m² without prophylactic G-CSF experienced with a median of 7 days with granulocytes less than 500 cells/mm³ (6). It should be noted that, despite this difference, the incidence of febrile neutropenia was low and similar in both trials, occurring in approximately 5% of all cycles delivered.

RESULTS FOR TAXOL AS SALVAGE THERAPY

This study is still sufficiently recent that estimates of rates of response and toxicity may prove to be labile. As of September 1, 1992, 228 cycles of Taxol had been delivered. The median number of cycles per patient is four (range, 1–10). Because we expected more severe hematologic toxicity in patients with prior chemotherapy, we chose a starting dose of 200 mg/m² by 24-hour infusion each 21 days, using premedications and posttreatment rhG-CSF as in our previous study. Consistent with prior experience, the dose-limiting toxicity was myelosuppression, predominantly neutropenia. Fifteen of 228 cycles (7%) were associated with febrile leukopenia. This complication affected 18% of patients. The median number of days in this trial with an absolute neutrophil count less than 500 cells/mm³ was 4, compared with 3.5 in our previous study. In contrast with our experience in patients without prior stage IV chemotherapy, where only one of 28 patients developed notable thrombocytopenia, 10 of 51 patients who had had prior stage IV chemotherapy developed thrombocytopenia below 50 000 per mm³ after Taxol and therefore required dose reductions. Twenty-four of 51 patients (47%) have required dose reductions so far, the majority because of hematological toxicity. One patient required reduction of dose because of hepatotoxicity. Because of toxicity, no patient has yet been a candidate for dose escalation. Eleven patients have had their doses reduced to 180 mg/m², 11 to 150 mg/m², and two to 125 mg/m². The spectrum of other toxicity was similar to that observed in our earlier experience but was slightly more severe. Four patients had grade 3 or 4 mucositis, and four patients experienced grade 3 myalgias and arthralgias. Three patients, two of whom had received prior cisplatin and vinca alkaloid, had grade 3 peripheral sensory and motor neuropathy. These women complained of difficulty with fine-motor functions such as buttoning clothing and

putting on earrings, as well as disturbing and painful paresthesias of the distal extremities. Alopecia was universal, but four patients were noted to have regrowth of hair while being treated with Taxol at doses ranging from 150 to 180 mg/m². No significant cardiac or hypersensitivity toxicities were seen. One patient demonstrated a cutaneous recall reaction of a previous radiation dermatitis.

All 51 patients are evaluable for response: 11 have achieved partial remission (22%; 95% confidence interval, 11%–35%). Responses were observed in all sites of metastatic disease. They continue to evolve in the 23 patients still being studied, so the overall response rate may prove to be greater than the current estimate. Although it is too soon to estimate the median response duration, it is now in excess of 10 weeks. Of particular note is that responses have been seen as frequently in patients whose disease was sensitive to anthracycline–anthracenedione (5/27 = 18.5%) as in those whose disease was primarily refractory to these agents (4/22 = 18.1%). One patient whose cancer had been stable on doxorubicin, and one whose cancer had been stable on mitoxantrone, subsequently responded to Taxol. Among seven patients receiving Taxol directly after disease progression without an intervening time interval and/or other chemotherapeutic regimens, three achieved partial responses.

DISCUSSION

On the basis of the preliminary results of our first trial, which confirm the data from The M. D. Anderson Cancer Center (6), and the observation of activity of Taxol in the salvage setting, we believe that Taxol is a relatively safe and very active agent in the treatment of metastatic breast cancer. Of note is that the patients on our trials had many characteristics that are usually associated with a low probability of response, especially the presence of many sites of metastatic disease. One patient demonstrated a complete remission in a site of prior radiation treatment, which is unusual. Hence, our trials might be biased toward an underestimate of true response rates.

The use of rhG-CSF resulted in a brief duration of Taxol-induced neutropenia; additionally, the vast majority of patients had granulocyte recovery to greater than 1500 cells/mm³ by day 14. This observation might prove useful in designing a dose-intensive regimen in which Taxol is administered more frequently than every 3 weeks. Even if ongoing research establishes that there is no dose-response relationship for Taxol (once some threshold dose has been achieved), there still may be advantages to increasing the dose intensity by shortening the cycle length (14). Taxol doses of 200 mg/m² to 250 mg/m² administered over 24 hours are tolerable in most patients without extensive prior chemotherapy, and it is unlikely that major escalations in dose will be possible because neurotoxicity becomes dose limiting with repetitive dosing above 250 mg/m².

We are encouraged by the implications of these preliminary data regarding a lack of cross-resistance of Taxol

with doxorubicin. Patients who received doxorubicin in the adjuvant setting and those whose macroscopic tumors demonstrated resistance to this drug were still able to benefit from Taxol. This is puzzling because cross-resistance to vinblastine has been observed experimentally, suggesting a mechanism of resistance involving the multidrug resistance gene (15,16). The polyoxyethylated castor oil vehicle used to solubilize Taxol in our trial has been reported to reverse multidrug resistance (17,18), but the relevance of this observation to our results will require further study.

In any event, the ability of Taxol to kill breast cancer cells resistant to cyclophosphamide and doxorubicin suggests a future role for this agent in high-risk stage II disease. The combination of doxorubicin and cyclophosphamide is effective adjuvant treatment but does not cure all patients (19). We have recently explored a sequential approach to this two-drug combination, using doxorubicin as a single agent followed by high-dose cyclophosphamide plus rhG-CSF (20). The sequential approach has been suggested by mathematical modeling (14) and has proved more effective than strict alternation of drugs in a clinical trial (21). Hence, there may be advantages to Taxol sequenced with doxorubicin and cyclophosphamide as adjuvant chemotherapy in patients with a high probability of recurrence after local treatment of primary breast cancer. These considerations do not preclude a role for Taxol in classical simultaneous combinations with other agents, which is presently under active investigation, as discussed elsewhere in this issue.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Taxol in the Treatment of Lung Cancer

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Taxol in phase I studies demonstrated some activity against a variety of solid tumors. The drug has undergone evaluation in phase II studies. The results of the three phase II studies of Taxol in the treatment of lung cancer that have been completed are reviewed. In the studies, the Taxol dose was 200–250 mg/m² given intravenously over 24 hours administered every 3 weeks. All patients studied received no prior chemotherapy. In an Eastern Cooperative Oncology Group (ECOG) study, five partial responses (21%) were observed in 24 evaluable non-small-cell lung cancer (NSCLC) patients, and in the M. D. Anderson Cancer Center Trial, there was one complete response (4%) and five partial responses (20%) in 25 evaluable patients. Thirty-two evaluable patients with extensive-stage small-cell lung cancer (SCLC) received a maximum of four doses of Taxol in a study conducted by ECOG. In this study, patients could receive salvage chemotherapy consisting of etoposide plus cisplatin. The response rate was 34%. The major toxicity in all studies was leukopenia. Taxol appears to be clinically useful in the treatment of NSCLC, but more studies are needed to determine its activity in SCLC. [Monogr Natl Cancer Inst 15:177–179, 1993]

Lung cancer is one of the most common malignancies and causes of death from cancer in the United States. It is estimated that, in 1992, there will have been 168 000 new cases of lung cancer diagnosed and 146 000 deaths (1). Non-small-cell lung cancer (NSCLC) accounts for approximately 75%–80% of all lung cancers, and small-cell lung cancer (SCLC) constitutes 20%–25% of all cases.

The overall cure rate for patients with lung cancer is less than 13%. The poor survival rates reflect the advanced stage of the disease at diagnosis, the high recurrence rates associated with surgery and radiation therapy, and the inability of combination chemotherapy to prolong survival significantly.

Because most patients with lung cancer will ultimately have metastatic disease, there is a great need for effective systemic therapy as treatment. To improve the response rates and duration of responses of the systemic therapy and ultimately increase the survival of lung cancer patients treated, the identification of new drugs with significant activity against lung cancer is needed. The following is a review of the studies to date, evaluating the new drug Taxol¹ in the treatment of lung cancer.

Taxol is a novel diterpene plant product isolated from the western yew, *Taxus brevifolia* (2). It exerts its

cytotoxic effect by interfering with microtubule structure and function (3,4). Taxol in preclinical tumor models, both in vitro and in vivo, has demonstrated significant antitumor activity (5).

In a phase I study conducted at Johns Hopkins in which the drug initially was given as a 1-hour infusion and then as a 6-hour infusion every 3 weeks, the dose-limiting toxicity was leukopenia (6). The recommended phase II dose was 212 mg/m². Sensory neuropathy was frequent, total alopecia was common, and other toxicities included nausea and vomiting, mucositis, myalgias, and phlebitis. The frequent occurrence of hypersensitivity reactions necessitated prolonging the infusions and premedicating patients with corticosteroids, antihistamines, and H₂ blockers. The allergic reaction has been characterized as an anaphylactoid reaction associated with hypotension and wheezing. In this study, one patient with NSCLC had an objective antitumor response.

In another phase I study conducted at Albert Einstein using the 6-hour infusion every 3 weeks with premedication of the patients as noted above, there was no episode of anaphylaxis (7). The dose-limiting toxicity was peripheral neuropathy at 275 mg/m².

Because of the allergic reactions, other phase I studies used a 24-hour continuous-infusion schedule of drug administration to be given every 3 weeks (8). This, together with the premedication regimen, significantly reduced the occurrence of the allergic reactions. The dose-limiting toxicity was peripheral neuropathy at 275 mg/m². The recommended phase II dose was 250 mg/m² as a 24-hour continuous infusion, repeated every 21 days.

NON-SMALL-CELL LUNG CANCER

The results of two phase II studies of Taxol in patients with advanced NSCLC were recently published (9,10). One study, conducted by the Eastern Cooperative Oncology Group (ECOG), from June 1990 to March 1991, involved 25 previously untreated patients with NSCLC (9). These patients had measurable metastatic disease with an ECOG performance status of 0 or 1 and adequate bone marrow, kidney, liver, and cardiac function.

Twenty-four patients were considered evaluable. The ineligible patient did not have metastatic disease. The characteristics of the evaluable patients were as follows: sex: 17 males, 7 females; age: median, 61 years (range, 38–82 years); performance status: 9–0, 15–1; and prior radiation therapy: yes–8, no–16.

*See "Notes" section following "References."

Patients received Taxol 250 mg/m² intravenously over 24 hours every 3 weeks. There were five partial responses (21%) seen, lasting from 3.7 months to 15.4+ months. Two patients had stable disease (8%), and 16 patients had progressive disease. One patient was unevaluable because of early death. The median survival time was 24.1 weeks. The 1-year estimated survival rate for the patients on Taxol was 41.7%. The major toxicity was myelosuppression, mainly leukopenia (12.5%, grade 3; 62.5%, grade 4). One patient died of drug-related sepsis. Other grade 3 toxicities consisted of the following: neurologic (21%), cardiac (12.5%), infection (12.5%), pulmonary (12.5%), hepatic (8%), and gastrointestinal (8%). Most of the toxicities were reversible and tolerable with dose modifications of Taxol.

The other study was conducted by the M. D. Anderson Cancer Center and the Community Clinical Oncology Program between June 1990 and May 1991 (10). Twenty-seven previously untreated patients received Taxol 200 mg/m² intravenously over 24 hours every 3 weeks. Twenty-five patients were evaluable. Two patients were not evaluable; one developed a grade 2 allergic reaction, and the other died of an intercurrent stroke.

The patient characteristics were as follows: sex: 14 males, 11 females; stage: III-3, IV-22; age: median 59 (range, 44-74); performance status: 3-0, 13-1, 9-2; and prior radiation therapy: yes-9, no-16. One complete response (4%) and five partial responses (20%) were observed in the 25 evaluable patients. An additional seven patients (28%) had a minor response. The median duration of survival was 40 weeks. The dose-limiting toxicity was neutropenia. Forty-one of 52 courses (79%) of therapy were associated with grade 3 or 4 neutropenia. Eight patients (32%) had grade 2 neutropenic fever requiring antibiotics. One patient had septic shock (grade 4) and recovered. Nonhematologic toxicities included alopecia (68%), nausea and vomiting (64%), diarrhea (36%), myalgia/arthralgia/bone pain (36%), stomatitis (32%), and neuropathy (28%). These toxicities were all grade 1 or 2 except for one patient who had grade 3 stomatitis. No cardiac toxicity was seen.

SMALL-CELL LUNG CANCER

At the time of this report, only one study had recently been completed evaluating Taxol in the treatment of extensive-stage SCLC (11). From October 1990 to October 1991, ECOG entered 36 previously untreated extensive-stage SCLC patients into a study evaluating Taxol 250 mg/m² administered intravenously over 24 hours every 3 weeks. Patients were eligible for the study if they had the following: measurable, extensive-stage SCLC; adequate bone marrow, liver, renal, and cardiac function; ECOG performance status of 0, 1, or 2; and no prior chemotherapy or radiation therapy.

At the time of this study, because of a limited drug supply, patients could receive a maximum of four doses of Taxol as induction therapy even if they were responding to

the drug. Those patients with progression of their disease after one cycle of therapy or stable disease after two cycles of therapy, or who achieved only a partial response after four cycles of Taxol, were to receive salvage chemotherapy consisting of etoposide 120 mg/m² intravenously over 45 minutes on days 1, 2, and 3 and cisplatin 60 mg/m² intravenously as a short infusion on day 1. Cycles were to be repeated every 3 weeks. Those patients who attained a complete response with Taxol were to receive prophylactic whole-brain irradiation, 2500 cGy delivered in 10 fractions over 2 weeks (250 Gy/fraction).

Thirty-four patients were evaluable for toxicity, and 32 patients were evaluable for response. The patient characteristics were as follows: sex: 21 males, 13 females; age: median, 63 years (range, 40-78 years); and performance status: 9-0, 19-1, 6-2. Eleven partial responses (34%) were observed in the 32 patients evaluable for response. An additional six patients (19%) had stable disease. Three of these patients had a greater than 50% shrinkage of their tumor; however, there was no 4-week follow-up measurement for them to be considered partial responders. In addition, two patients had less than 25% shrinkage in their tumor size and, therefore, were switched to salvage chemotherapy after two cycles of Taxol. One other patient received one cycle of therapy and did not receive another dose of Taxol because of toxicity. The estimated median survival was 45 weeks. The major toxicity was leukopenia, grades 3 and 4, occurring in four patients (12%) and 19 patients (56%), respectively. Other grade 4 toxicity included pulmonary (three patients [9%]), cardiac (one patient [3%]), thrombocytopenia (one patient [3%]), stomatitis (one patient [3%]), and allergic reaction (one patient [3%]). One patient (3%) died of infection. This death was thought to be drug related.

FUTURE DIRECTIONS

In two phase I studies conducted at Johns Hopkins in which Taxol plus cisplatin with and without the administration of granulocyte-colony stimulating factor (G-CSF) was given to patients with advanced cancer, antitumor activity was seen in patients with NSCLC (12,13). Based in part on the results of those two studies, ECOG proposes to conduct a three-arm randomized phase III study in patients with advanced NSCLC comparing etoposide 100 mg/m² intravenously days 1, 2, and 3 plus cisplatin 75 mg/m² intravenously day 1 with Taxol 135 mg/m² intravenously over 24 hours plus cisplatin 75 mg/m² with Taxol 250 mg/m² plus cisplatin 75 mg/m² intravenously plus G-CSF. All cycles will be repeated every 3 weeks.

Other combination chemotherapy regimens being considered by the National Cancer Institute for phase I evaluation, and possibly in the treatment of lung cancer, include Taxol combined with one of the following drugs: 10-EDAM, topotecan, or etoposide in the treatment of lung cancer. Additional studies are planned to evaluate Taxol as a single agent in the treatment of extensive-stage SCLC to determine its true activity. More-

over, Taxol combined with etoposide plus cisplatin has been proposed for evaluation in extensive-stage SCLC patients.

In at least one study published thus far, Taxol has been shown to cause radiosensitization (14). This is due in part to the ability of Taxol to block and/or prolong cells in G₂ or M phase of the cell cycle. Based on this finding, phase I and II studies have been proposed to evaluate the drug given concurrently with radiation therapy in stage III NSCLC. Such studies involve the use of low-dose Taxol given frequently as well as higher doses (i.e., therapeutic) of the drug administered intermittently.

CONCLUSIONS

Taxol is a new agent that has activity against NSCLC. It appears as active as ifosfamide, vinblastine, and cisplatin, which have reported responses of over 20%. Additional studies are planned to evaluate Taxol as a single agent in the treatment of extensive-stage SCLC. However, the response rate of 34% is comparable with that reported for doxorubicin, vincristine, cyclophosphamide, and etoposide in the treatment of SCLC.

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NOTES

¹Taxol is used in this monograph to refer to the drug that now has the generic name paclitaxel and the registered trade name Taxol® (Bristol-Myers Squibb Company, New York, N.Y.).

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Phase II Evaluation of Taxol in Advanced Head and Neck Cancer: An Eastern Cooperative Oncology Group Trial

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The Eastern Cooperative Oncology Group (ECOG) is conducting a phase II trial of Taxol in patients with histologically confirmed, advanced squamous cell carcinoma of the head and neck. Patients entered in the study to date either had recurrent disease or were newly diagnosed with incurable local-regional disease or distant metastases. Prior chemotherapy was limited to induction or adjuvant chemotherapy at least 12 months prior to entry in the study. All patients had an ECOG performance status of 0 or 1 and measurable disease. The treatment schedule was Taxol 250 mg/m² by 24-hour continuous intravenous infusion followed by r-met Hu granulocyte-colony stimulating factor 5 µg/kg/day subcutaneous injection day 3 to 15 or until the absolute neutrophil count was greater than 1500. Cycles were repeated every 3 weeks. As of September 1, 1992, 27 patients were registered in the study. Of these, three patients were determined to be ineligible, and three were too early to evaluate. There were two early deaths, one definitely and one possibly drug related. Two complete and five partial responses have been observed. Twenty-three patients receiving 83 courses were evaluable for toxicity. Myelosuppression was the primary toxicity observed with 17 (74%) patients experiencing grade 3 or 4 leukopenia and with 20 (87%) patients experiencing grade 3 or 4 neutropenia lasting an average of 2 days (range, 1-4). Peripheral neuropathy occurred in nine patients (grade 1, five patients; grade 2, three patients; grade 3, one patient). Other infrequent toxicities were stomatitis, nausea and vomiting, and myalgias. This trial will continue until 30 eligible patients are accrued. The results to date indicate activity for this dose of Taxol in patients with squamous cell carcinoma of the head and neck. [Monogr Natl Cancer Inst 15:181-184, 1993]

Head and neck cancer represents 6% of newly diagnosed invasive cancers in patients in the United States annually. Thirty percent to 50% of these patients will die from their cancer within 3 years. Distant metastases can be found at the time of death in 47% of all patients with head and neck cancer. Furthermore, over 90% of patients with distant metastases also have uncontrolled local-regional disease (1). Thus, the development of effective systemic therapies for patients with head and neck cancer is clearly needed.

Antitumor activity in squamous cell cancer of the head and neck has been demonstrated for a number of

cytotoxic agents. Methotrexate, cisplatin, carboplatin, bleomycin, and 5-fluorouracil (5-FU) are the most commonly used agents; response rates range from 15% to 40%. Most responses are partial, and response duration is brief, 2 to 4 months (2,3). Combination chemotherapy regimens such as cisplatin plus 5-FU result in higher response rates than single agents in comparative trials with recurrent-disease patients but do not improve survival (4,5). When combination chemotherapy is used as induction or neoadjuvant therapy to treat advanced, resectable disease, response rates range from 70% to 90%. However, randomized comparative trials have not demonstrated survival benefit compared with standard treatment (6). Therefore, new agents need to be identified to alter the poor prognosis for patients with head and neck cancer.

Taxol¹ is a novel diterpenoid originally isolated from the bark of the Pacific yew, *Taxus brevifolia*. The drug is a complex ester, shown to be a taxane derivative containing a rare octan ring. Taxol affects cells in G2/M phase by promoting microtubule assembly and stabilizing the tubulin polymers against depolymerization (7,8). In preclinical testing, Taxol demonstrated antineoplastic activity against B16 melanoma, human MX-1 mammary tumor xenograft, L1210 and P388 leukemias, and the CX-1 colon and LX-1 lung tumor xenografts. In phase I trials, activity was observed in a number of solid tumors including head and neck cancer. The principal dose-limiting toxicity was reversible neutropenia. The recommended dose for phase II trials ranged from 200 to 250 mg/m² (9).

To determine if Taxol possessed antitumor activity against squamous cell carcinoma of the head and neck, a phase II trial was initiated by the Eastern Cooperative Oncology Group (ECOG). The regimen tested was Taxol 250 mg/m² by 24-hour continuous intravenous (IV) infusion on day 1 followed by granulocyte-colony stimulating factor (G-CSF) 5 µg/kg/day by subcutaneous injection starting on day 3. The rationale for employing G-CSF was the ability of this growth factor to ameliorate severe neutropenia and thus allow patients to receive repeated full-dose Taxol without treatment delays and with reduced risk of infection. The highest recommended dose of Taxol was selected for this trial to ensure a definitive evaluation.

PATIENTS AND METHODS

Eligible patients had histologically confirmed squamous cell carcinoma from any site in the head and neck, exclud-

*See "Notes" section following "References."

ing the nasopharynx. Two groups of patients were eligible: 1) patients with previously untreated disease—newly diagnosed patients with locally advanced, incurable disease or distant metastases; and 2) patients with local-regional recurrence or distant metastases after initial treatment with surgery or radiotherapy. Patients may have received prior induction or adjuvant chemotherapy if it was at least 12 months prior to entry in the study, but they must not have received prior chemotherapy for treatment of recurrent disease. Radiotherapy must have been completed 4 weeks prior to patient entry. There had to be interim disease progression if measurable disease was within an irradiated field. Measurable disease and an ECOG performance status of 0 or 1 were required. Hematologic parameters for study entry were white blood cell count equal to or greater than 3500 cells/ μ L, platelets equal to or greater than 100 000 cells/ μ L, hemoglobin equal to or greater than 10 g, serum creatinine less than 2 mg%, and total bilirubin less than 1.5 mg/dL. Blood work and tumor measurements needed to be obtained within 2 weeks of registration to be eligible. Patients with a history of congestive heart failure, serious cardiac arrhythmias requiring anti-arrhythmia medication, or a history of myocardial infarction within the past 6 months were not eligible. All patients gave informed consent according to institutional guidelines.

To reduce the risk of anaphylactic reaction, patients were premedicated with dexamethasone, diphenhydramine, and cimetidine prior to and during the Taxol infusion (10). Taxol 250 mg/m² was administered by continuous IV infusion over 24 hours. In-line filtration with a 0.2-micron filter was required. r-met Hu G-CSF was administered in a dose of 5 μ g/kg/day by subcutaneous injection starting on day 3 until the absolute neutropenia count (ANC) was greater than 1500 on two successive determinations or until day 15 if neutropenia did not occur. Treatment was repeated every 3 weeks. To monitor hematologic toxicity, a complete blood count with differential count was obtained three times a week starting on day 8 until G-CSF was discontinued.

Dose reductions were specified for hematologic toxicity and neurotoxicity. Taxol was reduced for the occurrence of grade 4 neutropenia (ANC <500) lasting longer than 5 days, or febrile neutropenia requiring hospitalization and antibiotics, or grade 4 thrombocytopenia (platelets <25 000). Doses were reduced as follows: first episode, 200 mg/m²; second episode, 170 mg/m²; third episode, 135 mg/m²; fourth episode, 110 mg/m². If grade 2 neurotoxicity developed, the Taxol dose was reduced to 135 mg/m². National Cancer Institute common toxicity criteria were used to grade side effects. Treatment was continued until progression of disease was documented.

Standard ECOG response criteria were used to assess response. Complete response was defined as the complete disappearance of all clinically detectable malignant disease for at least 4 weeks. Partial response required at least a 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions for at least 4 weeks without an increase of greater than 25% in size of

any area of known malignant disease or the appearance of new areas of malignant disease. Stable disease was defined as a decrease in measurable disease of less than 50% or an increase of less than 25% for at least 4 weeks. Progression of disease indicated a greater than 25% increase in size of malignant lesions larger than 2 cm², or a 50% increase in the product of the diameters if only one lesion smaller than 2 cm² was measurable, or the appearance of new malignant lesions.

RESULTS

Twenty-seven patients were registered in this study as of September 1, 1992. Patient characteristics are as follows: males/females, 20/7; performance status: 0, five patients, 1, 22 patients; primary sites: oral cavity 6, oropharynx 10, hypopharynx 1, larynx 9, parotid 1; prior treatment: surgery only 2, surgery plus radiotherapy 21, surgery plus radiotherapy plus induction chemotherapy 2, none 2; sites of measurable disease: local-regional 17, distant 6, local-regional plus distant 4.

Of the 27 patients registered, three patients are ineligible, three are too early to evaluate, and there were two early deaths prior to response assessment. One death occurred on day 5 from a myocardial infarction probably unrelated to Taxol, and the other patient death was on day 9 from sepsis during neutropenia. The patient suffering a myocardial infarction was found, in retrospect, to have new ischemic change on his admission electrocardiogram. Therefore, it is unclear what role, if any, Taxol may have had in this cardiac event. At this point in the trial, response is assessable in 19 patients. Including the two early deaths, a total of 21 patients should be used for the response rate determination. There were two complete responses, one of which was pathologically confirmed, lasting 23 and 29+ weeks, respectively, and five partial responses lasting 10+, 16, 19, 22, and 27 weeks, respectively. Three patients had stable disease, and nine progressed. Sites of response were as follows: irradiated local-regional disease, four patients; local-regional disease, no prior treatment, one patient; and distant disease (lung metastases), two patients. The responses were observed after one cycle of Taxol for four patients and after two cycles for three patients.

Toxicity data were available in 23 patients receiving 83 courses of Taxol. The primary toxicity was myelosuppression. The maximum grade of toxicity occurring in each patient for which at least one episode was recorded was as follows: leukopenia grade 3, eight (35%), grade 4, nine (39%); neutropenia grade 3, three (13%), grade 4, 17 (74%); anemia grade 2, nine (39%), grade 3, three (13%). The mean duration of neutropenia was 2 days (range, 1–4). Despite the high frequency of grade 4 neutropenia, only eight patients required hospitalization and antibiotics. Of these, four had Taxol dose reductions for subsequent courses.

Other toxicities were peripheral neuropathy that was mainly sensory in nine patients [grade 1, five; grade 2,

three; grade 3, one (diabetic)]. The three patients with grade 2 neurotoxicity all had dose reductions and no further worsening of signs and symptoms. Stomatitis occurred in three patients (grade 1, one; grade 2, one; grade 3, one). Mild nausea and vomiting were reported in six patients and mild to moderate myalgias in nine patients. Alopecia was universal. No patient refused treatment because of toxicity, and there were no delays in treatment for bone marrow recovery.

DISCUSSION

This trial will continue until 30 eligible patients are accrued, at which time the 90% confidence intervals will be calculated. Based on the results thus far, one can state that Taxol appears to have antitumor activity in squamous cell carcinoma of the head and neck at the dose level studied. A confirmatory phase II study is planned at Ohio State University. The 250 mg/m² dose was associated with acceptable toxicity because of the use of r-met Hu G-CSF, which effectively reduced the risk of infection by shortening the duration of neutropenia. It is unclear whether G-CSF had any effect on retreatment time because in trials without G-CSF, almost all patients recover from myelotoxicity by day 22. One must, however, take into account the characteristics of the patients entered into this trial—excellent performance status and minimal prior treatment. Because of frequent, severe bone marrow toxicity, this high dose of Taxol with G-CSF support cannot be recommended for poor performance status and heavily pretreated patients.

A number of issues will need to be addressed in future trials of Taxol in patients with head and neck cancer. One is the question of a dose-response effect. Responses have been observed in other solid tumors, notably ovarian cancer, at lower doses, 110–135 mg/m² (11). Because of Taxol's unique mechanism of action and the observation from preclinical and phase I trials that mean steady-state plasma concentrations exceed the level causing microtubule polymerization in vitro (7,8,12), lower doses may be equally effective. This is particularly important when considering combination therapy. The next step in Taxol development is to evaluate a combination of cisplatin and Taxol. Phase I trials have identified a maximum tolerable dose recommended for phase II trials of Taxol 250 mg/m² and cisplatin 75 mg/m² with r-met Hu G-CSF support (12,13). Taxol and cisplatin can both cause neuropathy. Patients with conditions that can lead to neuropathy, such as diabetes and chronic alcohol abuse, are predisposed to develop this toxicity (Rowinsky EK: unpublished data), which may become treatment limiting. The need to employ G-CSF to lessen bone marrow toxicity with Taxol at 250 mg/m² is costly. ECOG has, therefore, proposed to conduct a successor trial evaluating two doses of Taxol (135 and 200 mg/m²) in combination with cisplatin.

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Taxol in Malignant Melanoma

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Taxol is a major new antitumor agent with significant activity against a number of human cancers. Preclinical investigation demonstrated significant activity against B16 melanoma and against cells derived from melanoma in a human stem cell assay. To determine whether there are sufficient clinical phase II data for Taxol activity against melanoma to warrant phase III clinical trials, data from the three published trials of Taxol in patients with metastatic malignant melanoma plus data from an ongoing Albert Einstein Cancer Center study of Taxol plus granulocyte-colony stimulating factor were analyzed for response rate and quality. Of 73 evaluable patients, complete plus partial responses occurred in 12 (16.4%). An additional nine patients had objective responses not qualifying for partial response, and 10 others had stabilization of previously progressive disease. Two complete responders remain disease free at 33+ and 46+ months. Patients with stable disease, minimal response, or partial response had a median duration of response of approximately 5 months (range 1-17 months). Responses occurred in liver, lung, skin, and other tissues. Taxol as a single agent has activity comparable with that of dacarbazine, cisplatin, or interleukin-2 in metastatic malignant melanoma. Pilot studies of Taxol combinations are warranted. [Monogr Natl Cancer Inst 15:185-187, 1993]

Therapy of metastatic malignant melanoma has been hampered by the lack of availability of drugs with major activity against the disease. An overall response rate of 12% was recently reported for dacarbazine (1), and most combinations of drugs that include that agent have not resulted in significantly better results, with the possible exception of those that include tamoxifen (1) or interferon (2). Single-agent activity of cisplatin (3) and carboplatin (4) is similar to that of dacarbazine, and cisplatin combinations that do not include tamoxifen (5) or a chemoprotector (6) do not yield response rates greater than cisplatin or dacarbazine alone (3). Therefore, it is imperative that the search for new agents and new modalities for this disease continues.

Interleukin-2, with or without lymphokine-activated killer cells, has been shown to have activity against malignant melanoma in a variety of schedules (7-10), but that activity appears to be no greater than that of standard chemotherapeutic agents or interferon (11,12), although complete responses may be more frequently obtained with interleukin-2.

Preclinical studies of Taxol¹ demonstrated significant activity against B16 melanoma (13), and Slichenmyer and Von Hoff reported activity against melanoma in a human tumor stem cell assay equivalent to activity against breast and ovarian cancer-derived cells (14).

MATERIALS AND METHODS

All available clinical trials data on the activity of Taxol against metastatic melanoma were analyzed for response rate and quality. The data were derived from three published phase I-II trials of Taxol in which patients with metastatic melanoma were included (15-17). In addition, melanoma patients who completed therapy on an ongoing Albert Einstein Cancer Center study of Taxol plus granulocyte-colony stimulating factor (G-CSF) were included in the analysis.

RESULTS

In an early phase I clinical trial of Taxol as a 6-hour continuous infusion, we treated one patient with metastatic malignant melanoma at a dose of 15 mg/m². The patient had no clinical response (18); however, the patient's melanoma cells obtained from a pleural effusion were sensitive to Taxol in vitro (18). In a subsequent 24-hour infusional phase I trial of Taxol (15), we observed a partial response in four of 12 melanoma patients who had received Taxol, 200-275 mg/m². Four of the 12 had received prior chemotherapy, and one of those responded to Taxol. The three other Taxol responders had not been previously treated. The magnitude of the responses ranged from 64% to 80% tumor reduction, although response duration was brief, ranging from 12 to 22+ weeks.

Our phase I studies led us to conduct a phase II trial of Taxol (250 mg/m² as a 24-hour infusion given every 3 weeks) under sponsorship of the Eastern Cooperative Oncology Group (ECOG) (16). Four of 28 evaluable patients had a major response, and three were complete. One complete response was terminated by meningeal carcinomatosis at 3 months, but the others continued at 33+ and 46+ months. These complete and partial responses in this group of previously untreated patients occurred only in patients with skin and soft-tissue metastases, although responses in liver and lung were observed in our previous study (15). Subsequently, Legha et al. (17) treated 25 patients with metastatic melanoma with Taxol at the same dose and on the same schedule as the

*See "Notes" section following "References."

Table 1. Melanoma patients treated with Taxol

Study (ref.)	No. treated	Complete response	Partial response	Minor response	Stable disease	Progressive disease	Not evaluable
Albert Einstein phase I (18)	12		4	2	2	3	1
ECOG phase II (16)	34	3	1	2	2	20	6*
M. D. Anderson phase II (17)	25		3	4	4	14	
Albert Einstein Taxol + G-CSF†	10		1	1	2	5	1

*Four had anaphylactoid reactions to the first dose and were taken off the study.

†Einzig AI, Wiernik PH: In press. Proc ASCO, 1994.

ECOG study. They reported three partial responses and four lesser objective responses. They noted, as we did, that some minimal and partial responses were of significant duration.

Table 1 summarizes the Einstein, ECOG, and M. D. Anderson experiences with Taxol in melanoma. All patients were performance status 0-1, and except for four patients in the Einstein phase I study (15), all were previously untreated with chemotherapy. All patients were premedicated to minimize the likelihood of an anaphylactoid reaction, and all patients received Taxol as a 24-hour continuous infusion every 3 weeks at a dose of at least 200 mg/m². Of 73 evaluable patients, 12 (16.4%) had a complete or partial response. Nineteen other patients may have benefited by obtaining a minimal response or stable disease (Table 2). Table 3 shows that some responses in all categories were of major duration. Responses were noted in liver, lung, skin, soft tissues, and lymph nodes, and site-specific response rates were proportional to the frequencies of involvement at those sites in the study populations. Age and sex of responders were similar to those features of the entire study population.

DISCUSSION

These data suggest that Taxol has single-agent activity comparable with dacarbazine, cisplatin, and interleukin-2 in malignant melanoma. We conclude, therefore, that pilot studies of Taxol combinations are warranted in advanced melanoma.

Table 2. Response rates to Taxol in patients with melanoma

Number of patients treated	81
Number of patients evaluable for response	73
Major response (complete + partial)	12/73 (16.4%)
Minor response	9/73 (12.3%)
Stable disease	10/73 (13.6%)

Table 3. Duration of Taxol response in melanoma patients

Response	No. of patients	Median duration, mo (range)
Complete	3	33+ (5-46+)
Partial	9	5+ (3-17)
Minor	9	5+ (1-11)
Stable disease	10	5 (3-10+)

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Phase I Study of Taxol, Doxorubicin, Plus Granulocyte-Colony Stimulating Factor in Patients With Metastatic Breast Cancer

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The objective of this phase I trial was to determine the maximal tolerated dose (MTD) of Taxol and doxorubicin administered as a simultaneous intravenous infusion over 72 hours every 21 days. Granulocyte-colony stimulating factor (G-CSF) 10 $\mu\text{g/kg}$, was administered on days 4–18 of each cycle. The treated population consisted of metastatic breast cancer patients previously untreated with chemotherapy for metastatic disease, who had not received doxorubicin in the adjuvant setting and who had bidimensionally measurable disease. The MTD was determined to be 75 mg/m^2 of doxorubicin and 160 mg/m^2 of Taxol. The dose-limiting toxicity of the combination was clinical typhilitis in three of three patients. Other significant toxicities included grade 3 diarrhea at the higher dose levels and grade 4 neutropenia in all patients. Eighteen patients were treated on this initial phase I study. The overall response rate was 62%, with 6% complete responses and 56% partial responses. The combination of doxorubicin and Taxol by 72-hour continuous infusion with G-CSF is an active regimen in patients with metastatic breast cancer. [Monogr Natl Cancer Inst 15: 189–194, 1993]

Despite the responsiveness of metastatic breast cancer to a number of chemotherapeutic and hormonal regimens, long-term outcome remains poor with a median survival of 18–24 months. There is a compelling need to develop effective novel agents alone and in combination to improve current therapy.

Doxorubicin is the most active single agent for the treatment of breast cancer and results in remissions in 40%–57% of patients (1,2). A dose-response relationship has been demonstrated in both preclinical experiments (3) and clinical trials (4,5). The addition of granulocyte-colony stimulating factor (G-CSF) modifies the dose-toxicity profile of high-dose bolus doxorubicin by reducing the duration of the neutrophil nadir and the epithelial toxicities (mucositis, diarrhea, and desquamation). In one series, up to 125 mg/m^2 of doxorubicin was well tolerated on an every-other-week schedule in combination with G-CSF (6).

Taxol¹ is a novel antimitotic cytotoxic agent derived from the bark of the Western yew (*Taxus brevifolia*) that has been shown to have significant activity against refractory ovarian carcinoma (7,8). Unlike vinca alkaloids,

Taxol promotes microtubule assembly and stabilizes tubulin polymer formation. More recently, an objective response rate of 56% [including 12% complete responses (CR)] was reported in a group of 25 patients with metastatic breast cancer who were administered Taxol at a dose of 250 mg/m^2 as a 24-hour continuous infusion every 21 days (9).

Given the promising report of Taxol activity against advanced breast cancer, we initiated an investigation into the safety and efficacy of this new agent when combined with doxorubicin and G-CSF. Both cytotoxic drugs were delivered concurrently via 72-hour continuous infusions every 3 weeks. This scheduling was based on data suggesting reduced toxicity and potentially greater efficacy when compared with administration schedules over several hours. A phase I trial of a 120-hour continuous infusion of Taxol without G-CSF done at the Dana-Farber Cancer Institute found the maximal tolerated dose (MTD) to be 35 mg/m^2 per day (10). The choice of a 72-hour infusion was based on the common use of this duration for doxorubicin infusions and the practical limitations to longer duration therapy. Prolonged infusions of doxorubicin may diminish both cardiotoxicity and nausea and vomiting (11). Histamine release may be seen with rapid administration of both anthracyclines (11) and Taxol (12). Because histamine release may play a role in the cardiotoxicity of both agents (13,14), we hoped to minimize the risk of additive cardiotoxicity by prolonging the infusions and administering concurrent antihistamines.

Prolonged exposure of tumor cells to cytotoxic agents may mitigate the effects of multidrug resistance proteins (15,16). For vincristine, another microtubule-active agent, it has been shown that the net effect on cycling cells can be increased with prolonged exposure (17,18) and that doxorubicin resistance in human colon carcinoma cell lines may be reduced by increasing the duration of doxorubicin exposure from 3 hours to 7 days (16). Furthermore, some doxorubicin-resistant cell lines develop cross-resistance to Taxol via a P-glycoprotein-associated mechanism and vice versa (19–21). The mechanism of Taxol-induced cytotoxicity is incompletely understood. The observed arrest of growing cells in G2/M and the well-characterized effects on microtubule kinetics do not necessarily correlate with cytotoxicity. Rowinsky et al. (22) have demonstrated in ovarian tumor cell lines that both microtubule bundle formation and cytotoxicity are

*See "Notes" section following "References."

more dependent on the duration of exposure than on Taxol concentration.

The objectives of this phase I trial were to 1) determine the MTD of concurrent Taxol and doxorubicin administration given by 72-hour continuous infusion in combinations with recombinant G-CSF every 3 weeks and 2) to determine the dose-limiting toxicities of this combination.

PATIENTS AND METHODS

Patient Eligibility

All patients were evaluated at the National Institutes of Health (NIH) Clinical Center between April 1991 and April 1992. All patients had histologically proven adenocarcinoma of the breast with pathologic evidence of metastatic disease (M1, stage 4). Histologic specimens were reviewed by the NIH Pathology Department. Bidimensionally measurable disease was required for study entry. Patients must have received no prior chemotherapy for their metastatic disease and have had no prior treatment with doxorubicin. Prior adjuvant chemotherapy was acceptable as long as doxorubicin was not part of the regimen. Prior hormonal therapy or radiotherapy did not exclude patients from entry provided the radiation did not involve the cardiac field or exceed 10% of the total bone marrow. Karnofsky performance status had to exceed 70%. The white blood cell count had to be more than $3500/\mu\text{L}$, with platelet counts at least $100\,000/\mu\text{L}$. Hepatic transaminases were required to be less than 1.5 times normal and creatinine not more than 1.5 mg/dL or creatinine clearance more than 60 mL/min. Patients must have had no prior history of cardiac disease, including arrhythmias, or any conduction system abnormalities. A baseline cardiac gated blood pool scan and an electrocardiogram had to be normal (left ventricular ejection fraction $\geq 45\%$). Patients could not be pregnant, and all patients had to give informed consent. Concurrent chemotherapy, radiation therapy, or immunotherapy was prohibited.

Study Design and Conduct

All chemotherapy infusions were given to patients while they were hospitalized at the NIH Clinical Center. The first two cycles of chemotherapy for each patient were administered with continuous cardiac monitoring, with all first cycles being initiated in the intensive care unit. Premedications included 1) dexamethasone 20 mg po or IV, 14 and 7 hours prior to the start of the Taxol infusion followed by 10 mg po or IV daily during the infusion; 2) diphenhydramine 25 mg IV or po, 30 minutes before Taxol, then every 6 hours during the infusion; and 3) cimetidine 300 mg IV or po, 30 minutes before Taxol then every 8 hours during the infusion.

Both Taxol (provided by the Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, IND #22850) and doxorubicin were administered over 72 hours by continuous infusion through

separate lumens of a central venous catheter. Subcutaneous chamber catheters (Port-a-Cath) were not used because of uncertainties regarding drug mixing and compatibility. Taxol was prepared in glass or polyolefin solution containers, and a 0.22-micron filter was used for in-line filtration distal to the infusion pump. The Taxol infusions were prepared by diluting the total daily (i.e., a 24-hour) supply in 250 mL of 5% dextrose injection or 0.9% sodium chloride injection. No more than 25 hours elapsed from the time of Taxol preparation until the end of the 24-hour infusion. The dose escalation scheme held the Taxol dose constant at $160\text{ mg}/\text{m}^2$ until a doxorubicin dose of $75\text{ mg}/\text{m}^2$ was reached, at which point further escalation of the Taxol dose was attempted.

Recombinant human G-CSF (provided by the Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, IND #BB2704) $10\text{ }\mu\text{g}/\text{kg}$ was administered subcutaneously daily starting approximately 24 hours following completion of the chemotherapy infusions. G-CSF was continued daily until the absolute neutrophil count (ANC) exceeded $4000/\mu\text{L}$ on two successive determinations. An ANC exceeding $1500/\mu\text{L}$ and a platelet count of at least $100\,000/\mu\text{L}$ were required prior to beginning each cycle of treatment as well as resolution of all grade 2 or greater nonhematologic toxicities. Patients requiring more than a 2-week delay in therapy for any cycle were removed from the study. Dose modifications were permitted beginning with cycle 2 and consisted of a one-dose-level reduction for grade 4 thrombocytopenia or grade 4 neutropenia longer than 5 days in duration, and a two-dose-level reduction for grade 3 or 4 nonhematologic toxicity. Inpatient dose escalation was not permitted.

Dose escalation started at $160\text{ mg}/\text{m}^2$ of Taxol and $45\text{ mg}/\text{m}^2$ of doxorubicin, and doxorubicin was increased to a maximum of $75\text{ mg}/\text{m}^2$; finally Taxol was increased in $20\text{-mg}/\text{m}^2$ increments. Dose-limiting toxicity (DLT) was defined as any grade 3 or 4 nonhematologic toxicity, excluding nausea or vomiting controlled with antiemetics. Hematologic DLT was defined as an ANC less than $500/\mu\text{L}$ for more than 5 days, a platelet count of less than $20\,000/\mu\text{L}$, or the inability to deliver full-dose chemotherapy on day 22 for cycle 2.

Patients were evaluated with a history and a physical exam prior to the start of each cycle, and all toxicities were evaluated and recorded. Toxicities were graded according to the NCI Common Toxicity Criteria. A complete blood count with differential count was obtained three times a week (Monday, Wednesday, and Friday) to document the duration of the neutrophil nadir. Liver function tests, blood urea nitrogen, creatinine, urinalysis, and electrolytes, including calcium and magnesium, were obtained every 3 weeks. A cardiac gated blood pool study was obtained prior to study entry and then after every third cycle up to a cumulative doxorubicin dose of $400\text{ mg}/\text{m}^2$, after which it was obtained prior to each cycle.

The extent of disease was documented by physical examination every cycle, and appropriate radiologic studies were performed at study entry [including at least a chest

roentgenogram, a chest computer tomography (CT) scan, an abdominal CT scan, and a bone scan]. The relevant imaging studies were repeated every three cycles, at which time a full assessment of antitumor response was completed. A CR was defined as the disappearance of all symptoms and radiologic findings related to cancer lasting at least 4 weeks. A partial response (PR) required at least a 50% reduction in the sum of the products of the longest perpendicular diameters of all bidimensionally measurable lesions lasting at least 4 weeks. A minor response required at least a 25% reduction in the same parameters. Because of the limitations in Taxol drug supply, all patients were required to have a minor response in order to continue in the study beyond three cycles. Patients with stable disease after three cycles of therapy were removed from the study.

RESULTS

Eighteen patients were entered into this initial phase I study. Table 1 summarizes the patient characteristics.

Dose Escalation

For the initial three dose levels studied, the Taxol dose was fixed at 160 mg/m², and the doxorubicin dose was escalated from 45 mg/m² to 75 mg/m² (see Table 2). At dose-level 4, Taxol was escalated to 180 mg/m² in combination with 75 mg/m² of doxorubicin, which induced DLT in three of three patients. The DLT was reversible grade 3 diarrhea and abdominal pain. Significant thickening of the cecum consistent with typhlitis was documented by abdominal CT scan in all three patients. The marked increment in clinical toxicity observed from this relatively small increase in Taxol dosage could not be explained by any apparent patient selection bias in the groups treated at these two dose levels. All three patients recovered fully without surgical intervention. Following full recovery,

Table 1. Patient characteristics

Number of patients	18
Prior adjuvant chemotherapy	4
Prior hormonal therapy	7
Median disease-free interval, mo	26
Estrogen receptors	
Positive	10
Negative	8
Progesterone receptors	
Positive	13
Negative	5
Sites of disease	
One	5
Two	6
Three or more	7
Liver disease	
Yes	10
No	8
Bone disease	
Yes	8
No	10
Soft-tissue disease only	2

Table 2. Dose-limiting toxicity

	Doxorubicin, mg/m ²	Taxol, mg/m ²	Patients with DLT
Level 1	45	160	1/6
Level 2	60	160	0/3
Level 3	75	160	0/6
Level 4	75	180	3/3

these patients were retreated with a two-dose-level reduction without recurrence of the gastrointestinal toxicity. The MTD of Taxol in combination with doxorubicin 75 mg/m² and G-CSF on this schedule was 160 mg/m².

Toxicity

This combination of Taxol and doxorubicin was generally well tolerated. There was one episode of ventricular fibrillation that was secondary to profound hypokalemia due to chronic diarrhea. This patient was successfully resuscitated and continued with treatment without recurrent cardiotoxicity. Overall clinical toxicities are summarized in Table 3. As expected, grade 4 neutropenia and alopecia were the most common toxicities, occurring in all patients. The median duration of grade 4 neutropenia was 3 to 5 days for all cycles delivered. Thrombocytopenia and anemia were also common and cumulative over the course of multiple treatments. Grades 2 and 3 diarrhea, mucositis, and myalgias/arthritis occurred in approximately one half of patients. The last may be partly related to the G-CSF. Nausea and vomiting were infrequent and generally mild. Peripheral sensory neuropathy was persistent in only seven patients and did not result in functional impairment. Electrolyte abnormalities were correlated with the presence of diarrhea. The only toxicities that correlated with the dose level of Taxol and doxorubicin were diarrhea and typhlitis as described above. The other toxicities occurred at all dose levels studied.

Cardiac toxicity was minimal, with three patients developing asymptomatic bradycardia (heart rate <60 beats/min) that abated when the infusions were com-

Table 3. Clinical toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Alopecia	0	18	0	0
Arthralgia	2	8	0	0
Bradycardia	3	0	0	0
Other arrhythmias	0	0	0	1
Diarrhea	4	6	5	0
Mucositis	1	11	4	0
Nausea	3	5	4	0
Vomiting	3	3	1	0
Peripheral neuropathy	6	5	0	0
Magnesium	3	6	0	0
Potassium	4	6	2	1
Leukopenia	0	0	0	18
Neutropenia	0	0	0	18
Anemia	0	5	10	3
Thrombocytopenia	2	2	4	9

pleted. No patient developed ventricular arrhythmias or heart block during Taxol and doxorubicin administration. One patient had an anaphylactoid episode minutes into the second cycle of treatment. This was manifested by flushing, substernal chest pain, and shortness of breath. An electrocardiogram showed T-wave inversions in the anterior leads, which reverted to normal within hours. This episode occurred 9 hours after the patient had received her last preinfusion dose of dexamethasone. On recovery, this patient was premedicated with dexamethasone, diphenhydramine, and cimetidine, and the infusions were resumed without further difficulty. No anaphylactoid episodes were seen in patients who began treatment with Taxol and doxorubicin within 7 hours of dexamethasone administration.

Responses

The overall response rate in these 18 patients with bidimensionally measurable disease was 62% (see Table 4). One patient (6%) achieved a CR, and 10 (56%) achieved a PR. The one CR occurred in a patient with supraclavicular and mediastinal adenopathy as her only sites of disease. The median duration from achievement of best response to disease progression for patients with a CR or PR has not yet been reached but is in excess of 8 months. The duration of the CR is longer than 12 months to date. The median time to achievement of a PR or a CR was 5 months.

DISCUSSION

We have treated 18 chemotherapy-naïve metastatic breast cancer patients with concurrent 72-hour continuous infusions of Taxol and escalating doses of doxorubicin with G-CSF. In this phase I study, we have defined the MTD of Taxol as 160 mg/m² in combination with 75 mg/m² of doxorubicin. The limiting toxicities were diarrhea and abdominal pain in three of three patients. Grade 3 diarrhea occurred at the highest dose levels administered and led to repeated dose reductions in five patients. Abdominal CT evidence of cecal thickening in the setting of moderate to severe abdominal pain and grade 3 diarrhea led to the clinical diagnosis of typhlitis in the three patients treated with 75 mg/m² of doxorubicin and 180 mg/m² of Taxol. This DLT and the other episodes of grade 3 diarrhea were surprising because infusional therapy with Taxol or doxorubicin as single agents is primarily associated with upper rather than lower gastrointestinal

toxicity (23–25). Mucositis has been reported as the major DLT of repeated treatment with continuous-infusion doxorubicin (26). In contrast, diarrhea has been described in association with intravenous bolus administration of doxorubicin. Mild to moderate diarrhea has been described in one study as a consequence of a 5-day intermittent schedule with daily 6-hour infusions of Taxol (27). Typhlitis has not been reported in association with either single-agent Taxol or doxorubicin administration. Grade 4 neutropenia developed by day 6 to 7 of cycle 1 of Taxol/doxorubicin/G-CSF treatment in the three patients with clinical evidence of typhlitis but persisted for only 5 to 6 days in each case. This is in contrast to the more common clinical scenario in which typhlitis develops in the setting of prolonged grade 4 neutropenia. Hruban and coworkers have described pathologic evidence of epithelial gastrointestinal necrosis in two patients treated with 250 mg/m² of Taxol by 24-hour continuous infusion (28). These findings were also associated pathologically with the accumulation of polymerized microtubules, suggesting a direct cytotoxic effect of Taxol (28). We would suggest that the typhlitis observed in this study was likely caused by the combination of severe neutropenia and direct toxicity of Taxol and doxorubicin in bowel mucosa. Notably, all three patients recovered completely without surgical intervention and did not develop recurrent episodes with a two-dose-level reduction for cycle 2.

On this protocol, patients were treated with the purpose of maximizing dose intensity. Hematologic toxicity was significant, with all patients developing grade 4 neutropenia of 3 to 5 days' average duration. Interestingly, neutropenia was dose limiting in only one of 18 patients. However, 47% of all cycles required hospitalization for fever and neutropenia despite treatment with G-CSF. In only 8% of cycles was a source of infection documented, and no patient developed clinical septicemia.

Significant cardiac toxicity was not observed in this study despite the known potential cardiac toxicity of Taxol and doxorubicin as single agents (14). Asymptomatic bradycardia occurred in three patients during treatment but resolved on completion of the 72-hour infusions. The only severe cardiac toxicity, a ventricular fibrillation arrest, occurred as a result of chronic diarrhea-induced hypokalemia. A diminution in left ventricular ejection fraction was seen in two patients and was consistent with the toxicity associated with repeated anthracycline administration. No significant heart block or any ventricular tachycardia was observed. Asymptomatic T-wave inversions were noted on electrocardiograms in three patients during the 72-hour infusions but reverted to normal within hours of completing therapy. No additive or synergistic cardiac toxicity from this drug combination was apparent in this study.

The overall response rate of 62% in this group of metastatic breast cancer patients previously untreated with chemotherapy is within the range seen with other active combination regimens (42%–82%) (29). The median duration of response (time from best response to progression)

Table 4. Responses

Response rates	Patients (%)
Overall	11/18 (62)
CR	1/18 (6)
PR	10/18 (56)
Minor	4/18 (22)
Stable disease	3/18 (16)

for patients achieving a CR or PR has not yet been reached but is in excess of 8 months to date. The responses, therefore, are durable, with no significant differences in duration yet apparent between the estrogen receptor positive versus estrogen receptor negative patients.

Although the objective response rate in this phase I trial is no better than that reported for Taxol alone at a different dose and schedule (9), it is premature to draw conclusions about the efficacy of Taxol plus doxorubicin combination therapy for metastatic breast cancer. Further investigation into the cellular, pharmacologic, and clinical interactions between these highly active agents is warranted. Trials to optimize the sequence, dose, and schedule of administration of these drugs in metastatic breast cancer are planned.

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Taxol Commercial Supply Strategy

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Evidence of Taxol's safety and efficacy for treatment of refractory ovarian cancer convinced the National Cancer Institute (NCI) to seek a pharmaceutical partner and approval. After an open competition, NCI entered a Cooperative Research and Development Agreement with Bristol-Myers Squibb Company (BMS) to obtain approval of a New Drug Application (NDA) so that Taxol could be marketed as well as to provide supplies for clinical trials and compassionate use. To assure a successful commercialization of Taxol, BMS developed a strategic plan for expanding drug supplies. The strategy included immediately increasing the amount of Taxol derived from yew bark and establishing a broad research program to evaluate alternative sourcing options and their commercial feasibility. The options included precursor isolation and semisynthesis, yew plantations for biomass production, plant cell culture, and total synthesis. A number of both academic and industrial investigators, already interested in various Taxol supply issues, were enlisted for collaborations with the company. Progress on this research during the first 18 months has enabled BMS to do the following: 1) double the yield of Taxol from bark extraction; 2) exceed NCI's request for drug supplies in 1991, permitting establishment of an ovarian cancer treatment referral center (TRC) with a national network of comprehensive cancer centers; 3) increase NCI supplies from 5000 to 50 000 vials/month in 1992, permitting establishment of TRC protocol for breast cancer; 4) identify several potentially viable alternative sources; 5) schedule production of large amounts of Taxol by precursor conversion during 1993; and 6) ensure that sufficient quantities of the product will be available for treatment and continued clinical research. The Taxol NDA was filed in July 1992. The unprecedented alliance of various government agencies, academic institutions, and the private sector has accelerated development of this important new cancer drug beyond expectation and will ensure its sustainable availability from various sources. [Monogr Natl Cancer Inst 15:195-198, 1993]

Taxol¹ has been under investigation at the National Cancer Institute (NCI) for over 20 years. Supply shortages severely limited clinical research because of the low concentration in the bark of the Pacific yew, the arduous isolation process, and the difficulties in formulating such an insoluble compound. By 1989, NCI believed that evidence of Taxol's safety and efficacy for the treatment of refractory ovarian cancer (1-3) warranted submission of a

New Drug Application (NDA) for Food and Drug Administration (FDA) approval so that the drug could be marketed. NCI sought to establish a treatment referral center and a network of participating comprehensive cancer centers to provide Taxol therapy for appropriate ovarian cancer patients until the NDA was approved. Preliminary indications of Taxol's activity in other tumor types suggested that extensive clinical research to determine its full spectrum of activity and optimal treatment regimens would be required. Additional research on the compound's novel mechanism of action and other nonclinical parameters, such as exploring alternative sources, was also deemed necessary.

To accomplish these goals, and to ensure wide commercial distribution through marketing of the approved product, NCI sought a qualified pharmaceutical industry collaborator (4) and in January 1991 signed a Cooperative Research and Development Agreement (CRADA) with Bristol-Myers Squibb Company (BMS). BMS was chosen in an open competition to be NCI's partner because of the company's broad experience in natural products, longstanding success in cancer drug development, and submission of an aggressive Taxol development plan.

The primary provisions within the CRADA stipulate that, in exchange for exclusive access to NCI clinical and preclinical data necessary to obtain approval from the FDA for an NDA, which the company agreed to prepare and support as soon as possible, BMS also will provide Taxol to NCI free of charge for clinical research and compassionate use programs, and will investigate alternative sources of Taxol.

A joint steering committee was established to oversee the CRADA. The committee's responsibilities included planning and coordinating clinical development and supply allocations. The CRADA was necessary because NCI's mission does not encompass the commercialization of drugs. The agency has neither the resources nor the expertise to make pharmaceutical products available on a commercial scale. The Federal Technology Transfer Act authorizes the use of CRADAs to encourage public and private partners to enter collaborations of this nature.

To fulfill CRADA requirements and to ensure the successful commercialization of Taxol, BMS developed a comprehensive sourcing strategy for increasing drug supplies. This strategy provided for an immediate expansion of Taxol derived from Pacific yew bark, to date the only approved source of Taxol for human use. A broad research program to evaluate simultaneously several long-term alternative sourcing options and their commercial feasibility was defined.

*See "Notes" section following "References."

EXPANDED PRODUCTION FROM YEW BARK

From the early 1980s to 1991, approximately 150 000 lbs of Pacific yew bark was collected with the cooperation of the U.S. Department of Agriculture (USDA) Forest Service. Taxol was produced at an average rate of 1 kg every 2 years. It became apparent that to fulfill the increased requirements for an expanding clinical research program as well as a plan for expanded access to Taxol therapy through a treatment referral center program, a significant increase in the bark collection program would be required. The Secretary of Health and Human Services, the Secretary of Agriculture, and the Secretary of the Interior acknowledged this increased need by signing a Memorandum of Understanding to promote cooperation among the three departments on the Taxol project.

Cooperative agreements with the USDA Forest Service and the U.S. Department of the Interior Bureau of Land Management granted BMS, as NCI's sole partner, exclusive access to Pacific yew bark for 5 years. The intent of the agreements is to facilitate an expanded bark harvest for use in a process qualified to produce a drug for clinical research and patient therapy. In exchange, BMS agreed to fund research on yew ecology and conservation guidelines for preservation of the yew species. BMS also agreed to sponsor a Pacific yew tree inventory and the preparation of a programmatic Environmental Impact Statement to assess the effect of this short-term, large-scale bark harvest. Also, BMS agreed to reimburse both federal agencies for bark transfer costs and other administrative costs, such as law enforcement, incurred on the Taxol project.

Another vital collaborator in the yew bark collection program has been Hauser Chemical Research Company. Experienced in producing small amounts of Taxol for NCI, Hauser agreed to establish a large collection effort to harvest and process bark for production of Taxol suitable for human use. With the help of the Forest Service and the Bureau of Land Management, Hauser collected more than 850 000 pounds of dried bark from public lands and a similar amount from private lands in 1991. In addition, Hauser process improvements doubled the yield of Taxol from bark extraction to the current level of 1 kg of drug from approximately 16 000 lbs of bark. The continued success of this program in 1992 enabled BMS to increase Taxol supplies further, from 5000 to 50 000 vials per month. These increased supplies allowed NCI to establish a nationwide network of participating comprehensive cancer centers through the treatment referral center program for ovarian cancer and will also support the network's use of a protocol to treat breast cancer patients.

ALTERNATIVE SOURCE RESEARCH

Although expansion of Taxol production from bark was an immediate imperative, BMS recognized that bark was a finite resource. As a result, the company began a program to identify alternative, long-term, commercially viable Taxol supply sources. Significant progress in exploring

these potential alternative sources has been made through various collaborations with a multitude of academic and industrial investigators. Sources that appear promising include precursor isolation and semisynthesis, yew cultivation for biomass production, plant cell culture, and total synthesis.

Semisynthesis

It is anticipated that semisynthesis of Taxol from the precursor, 10-deacetylbaccatin III (10-DAB), will be the first alternative source to be commercialized. Large quantities of 10-DAB extracted from renewable biomass (needles and twigs) collected from the European *Taxus baccata* and the Himalayan *Taxus wallichiana* yews will be produced for BMS by Indena, a company in Milan, Italy, specializing in natural products.

BMS has licensed methods developed by Dr. Robert Holton at Florida State University in Tallahassee to convert this natural precursor to Taxol and is supporting his research efforts to further improve the process. In mid-1993, BMS successfully completed the scale-up of Taxol production by semisynthesis for commercialization. Filing of the Supplemental New Drug Application is scheduled for the end of 1993.

Yew Cultivation

BMS is sponsoring a research program at the Weyerhaeuser Company to determine the best species of yew for cultivation of biomass for Taxol production. Methods to enhance both the seedlings' growth rate and Taxol (or precursor) content in the selected species are also being studied. However, because cultivated biomass will be needed for Taxol production before the research can be completed, over 5 million seedlings of a readily available ornamental cultivar were planted. The dedicated crop will be ready for harvesting in 1994. Subsequent crops should be enhanced by results of the research in progress.

Investigators at the University of Mississippi, under BMS sponsorship, are developing a system for the use of ornamental yew nursery stock clippings as a sustainable and economic source of Taxol. Collaborations with the Ohio Agricultural Research and Development Center and Zelenka Nursery have focused on mechanical harvesting, drying, and storage techniques for preservation of Taxol content.

Plant Cell Culture

To date, no pharmaceutical products are produced on a commercial scale by plant cell culture techniques. BMS, however, is exploring this approach to Taxol production, encouraged by the control, adaptability, and potential similarity to well-established fermentation and mammalian cell culture techniques. The company established a collaboration with Phyton Catalytic, Inc. (PCI), a plant biotechnology company. Early results from PCI, confirmed by BMS, are promising and warrant continued development. In addition, BMS is sponsoring a long-

standing research effort on cell lines development in the laboratories of Dr. Richard Arteca at Pennsylvania State University.

Total Synthesis

Total synthesis of the complex Taxol molecule has not been achieved despite the efforts of many academic laboratories. BMS is currently sponsoring well-advanced research at Ohio State University by Dr. Leo Paquette and at Stanford University by Dr. Paul Wender. Significant progress has been reported by Dr. Wender (5) on the ring system synthesis, which uses the readily available pine tree constituent, pinene, as a starting material.

The tricyclic core of the Taxol molecule, including the complete functionality and stereochemistry of the Taxol A ring, can be synthesized from pinene in eight steps. Further studies to introduce certain groups of the B and C rings are in progress. Once the synthesis is complete, the commercial feasibility of this process will be determined. Additionally, the versatility of this and other total synthetic efforts, such as that of Dr. Holton's at Florida State

University, may prove to greatly facilitate synthesis of improved Taxol derivatives.

CONCLUSIONS

Encouraging results in the development of alternative sources of Taxol have allowed BMS to accelerate its plans to reduce reliance on yew bark. Before the end of 1993, the company will produce significant amounts of the drug by using semisynthesis and will file a Supplemental New Drug Application for commercial use of this method. In 1994, BMS expects to use bark for less than half the total Taxol requirement and only small amounts will be produced from bark in 1995. By 1998, BMS will be in a position to assess the various alternative options and produce Taxol from the most economical sources. Full implementation of this strategy is shown in Fig. 1.

The success of this program can be attributed to the unprecedented alliance of government agencies, academic institutions, and the private sector. The synergy of this coalition has accelerated the development and increased availability of an important new cancer drug.

Percentage of Total

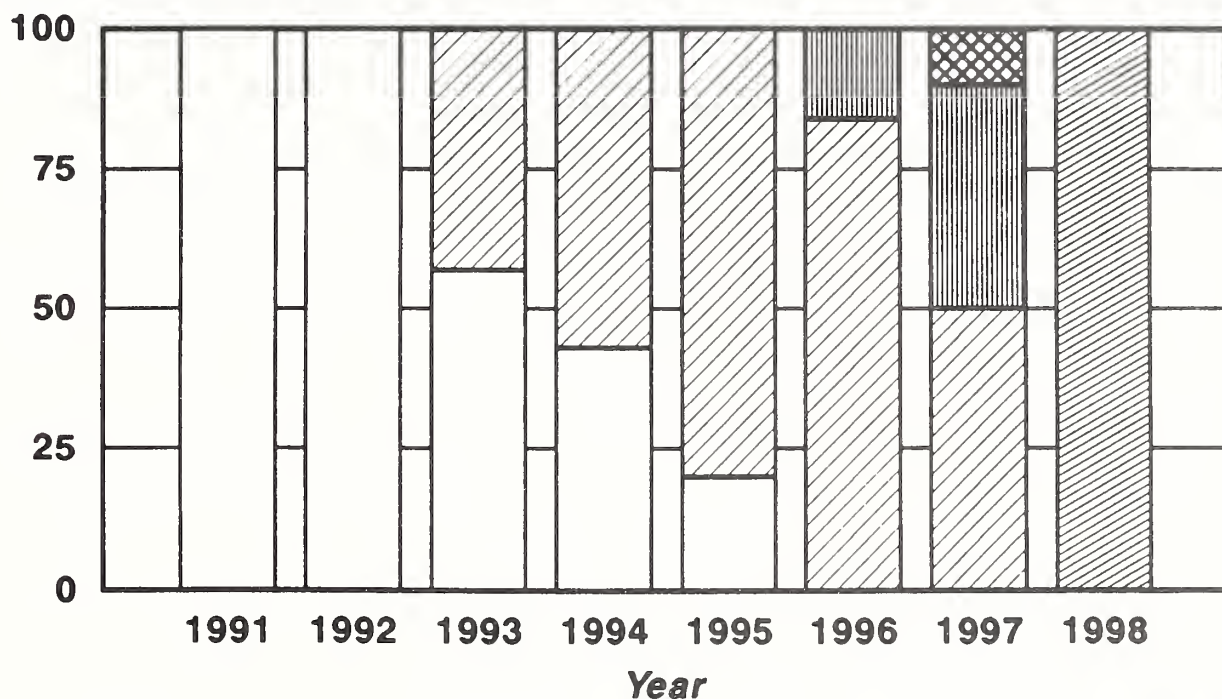


Fig. 1. Taxol supply situation.

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